BONE TUMORS

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With 220 Illustrations

Second Edition

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Preface to Second Edition

Some six years have elapsed since *Bone Tumors* was published with a view to conveying a practical working knowledge of the benign and malignant tumors of bone, emphasizing accurate diagnosis and therapeutic indications. Progress in the utilization of this essential information has been gratifying as has the reception of the work by the medical profession generally

In preparing this revised edition the accrued observations and advances of the past several years have been incorporated in the subject matter presented so that virtually every chapter has been modified to some extent. An appreciable number of new illustrations, both roentgenograms and photomicrographs have been added A brief introductory chapter directed to clinicians and pathologists has also been added as a guide to the appropriate management of bone lesions that may be tumors. To enhance the usefulness of the book further a chapter on Tumors of Periosteal Origin has been introduced, and a discussion on Tumors of Synovial Joints Bursae and Tendon Sheaths has been added to the Appendix as collateral material Finally in response to many requests, I have amplified the discussion in the Appendix dealing with Some Non-Neoplastic Lesions of Bone Which May Be Mistaken for Tumors.

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Preface to First Edition

This book is the outgrowth of a long series of studies on primary tumors of bone pursued in collaboration with Dr Henry L. Jaffe during the period 1938-1948 while working at the Hospital for Joint Diseases in New York. These investigations were based upon the accumulated material of the hospital richly supplemented by case material from other sources much of it referred for consultation. As a result, certain old ideas were of necessity revised and a number of new clinical radiologic and pathologic concepts were advanced which found expression in individual papers dealing with many of the benign and malignant primary bone tumors and also with a number of non-neoplastic lesions of bone sometimes mistaken for tumors. To designate some of these distinctive lesions appropriately new names had to be coined, such as benign chondroblastoma chondromyxoid fibroma, non-osteogenic fibroma fibrous dysplasia, eosinophilic granuloma and aneurysmal bone cyst which have since gained wide acceptance.

I have been repeatedly urged by my colleagues in pathology radiology and orthopedic surgery particularly to make the individually published papers dealing with bone tumors more readily available by incorporating their subject matter into a monograph In the course of preparation of this book, the previously published articles have all been revised and brought up to date while certain new sections dealing with subjects not previously covered namely osteogenic sarcoma tumors of vascular fat-cell and nerve origin so-called adamantinoma of limb bones carcinoma metastatic to bone and the skeletal manifestations of tumors of hematopoietic origin have been added to enhance its usefulness and give more complete coverage of the field. Further since as much mischief is done by over diagnosis as by failure to recognize malignant tumors promptly a section has been added as an appendix, dealing with certain non-neoplastic lesions of bone which are sometimes mistaken for tumors e.g fibrous dysplasia eosinophilic granuloma, aneurysmal bone cyst and myositis ossificans, among others. With this exception no extraneous subjects have been introduced.

Emphasis has been placed throughout the book upon accurate diagnosis as a basis for appropriate treatment through familiarity with the distinctive features of each of the neoplasms presented. The time is long since past when it might be said with some justification that the clinical history the x ray picture or the response to treatment were more *valuable than the pathologist's opinion* Inasmuch as the usefulness of some of the existing books in the field is seriously marred by pathologic inaccuracies, I have made it a special point to discuss or illustrate only cases in which I have had the opportunity personally to establish or verify the diagnosis by tissue examination On the other hand it is not intended to imply that the pertinent clinical data and the roentgenograms are not important in an analysis of the problem in diagnosis and therapy although there are some pathologists naive enough to believe that one can make sound recommendations in regard to treatment from a biopsy slide alone. In this book, illustrative roentgenograms have been freely utilized as a uniquely useful tool in determining the extent and topography of various skeletal lesions, and in judging their probable behavior on the basis of what they have done to the bone

The relatively few blood chemical alterations that are of diagnostic importance have been considered in connection with each of the neoplasms concerned. It requires no lengthy dissertation to point out that in osteogenic sarcoma the serum alkaline phosphatase value is often elevated that in approximately half the cases of multiple myeloma one observes hyperglobulinemia and/or hypercalcemia that in carcinoma metastatic to the skeleton rapid demineralization may result in moderate hypercalcemia and that in the case of prostatic carcinoma specifically one commonly observes increased alkaline and acid phosphatase activity

Problems in therapy have likewise been considered in relation to each of the neoplasms discussed. The emphasis throughout has been placed upon sound therapeutic indications and beyond these I do not feel that a competent surgeon needs to be told how to perform thorough curettement, resection, or *amputation* any more than a skilled radiotherapist requires details of technique in most situations.

In the interest of clarity and conciseness the regional treatment of bone tumors has been rejected as entailing unnecessary and confusing repetition Further no attempt has been made to employ considerations of embryologic development as window dressing, although a few specific allusions have been made when indicated. In the matter of bibliography selected articles have been cited and no attempt has been made to list all of the pertinent references. The literature pertaining to many of the bone tumors has become so voluminous, that it would be virtually impossible to catalogue it, even if it were desirable to do so

I am indebted to Ruth Cordish and Lloyd Matlovsky for their painstaking illustrating in the matter of x ray reproductions and photomicrographs to Dr Alex Griswold for his meticulous proofreading and general criticism of the text and to my numerous colleagues and friends in pathology radiology and orthopedic surgery who have generously placed much of the interesting case material at my disposal. It would not have been possible to complete this book in its present form without their sustained interest and gracious cooperation

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Foreword to Pathologists

It is my impression that standards in the reliable pathologic appraisal of tumors and tumorlike lesions of bone have risen perceptibly within the past six years since the first edition of this book appeared. In correspondence with pathologists throughout the country seeking help with their problems in this field I find fewer men who fail to display good insight and many more who are keenly aware of their responsibilities but want moral support or encounter atypical tumors or mavericks so to speak, for which they have no precedents in their own experience With reference to these unusual cases it has been my privilege to be of assistance in resolving some of the questions, and it is the accumulation and study of this valuable material that makes it possible in time to develop new concepts.

Although this is less complimentary I feel obliged to stress once again that there are still far too many pathologists who venture opinions having a bearing on treatment and prognosis (or expect me to do so) from slide interpretation alone without fully realizing the collateral importance of the pertinent roentgenograms and of an adequate history including the surgeon s findings. To function in this field simply as a slide reader without benefit of good clinical orientation can be disastrous at times since the location of a lesion or what it has done to the bone (as a portent of its growth potential and probable behavior in the future) can conceivably be as significant as its cytologic picture. For example the criteria outlined (in Chapter 14) for the recognition of early chondrosarcomas apply strictly to central cartilage tumors of bone and not at all to the growing cartilage caps of osteochondromas in young patients, or to periosteal chondromas or to extraskeletal cartilage tumors necessarily which have a different natural history To cite another instance in point a lesion of myositis ossificans at the height of its activity may appear ominous enough cytologically to suggest osteogenic sarcoma but only if one were uninformed as to the history and the location of the mass *outside* of the contiguous bone I am not unaware of the practical limitations of poor liaison in some hospital situations and of the time imposed by

a large volume, but it cannot be emphasized too strongly that this is one branch of pathology in which effective medical communication is of prime importance.

Getting down to more mundane considerations, it may be in order to comment briefly on the problems of obtaining satisfactory bone sections. Altogether I find that while some laboratories turn out consistently good or excellent bone sections many more leave a great deal to be desired By and large, a pathologist gets only as good a preparation from his tissue technician as he expects, and otherwise competent technicians can be taught to improve the quality of their bone preparations. Without going into details of procedure a few practical suggestions may be helpful Tissue blocks should be carefully trimmed, so as to be neither too large nor more than several millimeters in thickness, and here a band saw can often be used to advantage. Whenever possible bits of soft tissue that do not require decalcification should be processed separately since these afford the best cellular detail Not infrequently one has to dig them out of the bone lesion with a knife point. Fixation in Zenker's solution often yields better results than conventional formalin fixation but this is not essential. Also irrespective of whether one uses nitric acid or formic acid (in adequate volume) for decalcification, perhaps speeded up by an electrode device, or whether one resorts to modern chelating agents meticulous attention must be given to the determination of the earliest point of adequate decalcification. When a bone block can be readily pierced with a pin it is usually ready for cutting The time required obviously varies from specimen to specimen so that assembly line production methods will not do Inadequate treatment causes shattering of cement lines when the block is cut while overdecalcification (an equally common fault) tends to obscure cellular detail. In the matter of staining, my own preference is for a deep hematoxylin and a relatively light eosin stain

I am happy to comply with the suggestion made by some of my colleagues that I clarify my position in regard to frozen sections for the rapid diagnosis of bone tumors. I have long been accustomed to using this method to advantage as a guide to the choice of appropriate surgical procedure for a quick line on prognosis and at times, to obviate delay in doing amputation when this is clearly indicated One must be very wary however of jumping to serious conclusions from equivocal evidence It should be emphasized that in dealing with bone lesions, it is essential to counterstain with eosin in addition to using a nuclear stain (hematoxylin is preferred) since otherwise it is possible to overlook patches of osteoid or new bone At the same time I recognize readily that pathologists whose experience in this field is not very extensive might be reluctant to accept responsibility for a rapid diagnosis under these circumstances, and I do not believe that they should be required to do so

Finally I wish to state clearly my views on the value of needle biopsy of bone lesions. This approach to diagnosis has many strong adherents in Latin America (Argentina especially) and some in this country mainly in institutions with very large clinic populations and relatively few hospital beds, where they have made a virtue of necessity My personal impression is that the method has only limited usefulness when applied to bone tumors and specifically in lesions in vertebral

bodies (provided the operator is skillful in localization) with foci of metastatic carcinoma (where the finding of even a few cell nests affords an unequivocal diagnosis) and in some few primary tumors of strikingly uniform cytology such as myeloma or chordoma (in which one can often obtain a representative field of diagnostic value by random sampling) In most other situations, speaking quite candidly I dislike needle biopsy and shy away from it (if there is any alternative) in the belief that the meager cytologic picture thus obtained is frequently not representative of the lesion as a whole nor too informative and may in fact be misleading as often as it is helpful It s something like riding a bicycle with your hands tied behind your back it s a good trick, if you get away with it but if you hit an obstacle you re apt to fly over the handlebars and break your neck.

LOUIS LICHTENSTEIN

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I

General Remarks on the Clinical Management of Bone Lesions That May Be Tumors*

Before launching into specific details, it seems important at the outset for overall orientation to emphasize certain basic general principles entailed in the recognition and appropriate treatment of bone lesions that may be neoplasms. *(If any of these views are restated in subsequent chapters, the repetition is intentional and deemed justified by the importance of the points stressed.)*

1 If a patient complains of persistent pain swelling or limitation of motion *in an extremity or some other skeletal part,* obtain good roentgenograms promptly If these disclose a significant skeletal lesion that may be neoplastic, do not guess at its interpretation but obtain a reliable opinion. Roentgenograms are essential in determining the extent and topography of various skeletal lesions and in judging their probable behavior on the basis of what they have done to the bone. It must be recognized however that radiologic interpretation has its inherent limitations and that, as a rule biopsy is required for definitive diagnosis. Despite the impression that still prevails in some quarters, there are no pat formulas for the roentgen ray diagnosis of bone tumors, and most of the allegedly pathognomonic signs, while sometimes helpful, are often fallacious (see Chapter 2)

2. The problem in diagnosis should be analyzed before surgery is undertaken since the choice of procedure, whether it be conservative biopsy curettement, resection or amputation, varies with circumstances. Needle biopsy incidentally has only limited usefulness in the diagnosis of bone lesions. The planning of an advantageous approach often calls for good liaison between surgeon, radiologist and pathologist.

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* Lichtenstein, L. Primary Malignant Tumors of Bone CA A Bulletin of Cancer Progress 4: 1 17 1954

While this principle appears self-evident and is generally recognized as sound, in actual practice some men pay only lip service to it and seek advice after the fat is already in the fire, so to speak. An important corollary is that the pathologist must be more than a slide reader if he is to function efficiently in this field and should have the benefit of good clinical orientation before venturing an opinion as to diagnosis and/or prognosis.

3 Definitive treatment, whether by surgery or irradiation, should be predicated upon accurate pathologic diagnosis. The time is long since past when it might be said with some justification that the clinical history the roentgenogram, or the response to treatment was more valuable than the pathologist's opinion. I am unalterably opposed to blind irradiation of skeletal lesions believed to represent tumors except perhaps for palliation of far advanced malignant tumors in inaccessible sites. By the same token, I am categorically opposed to radical surgery undertaken on the strength of a roentgen-ray impression alone, however well founded it may seem. What appears to be an obvious osteogenic sarcoma, for example, justifying ablation of an extremity may conceivably prove to be a lesion of sclerosing metastatic carcinoma.

4 If roentgen therapy is the treatment of choice for whatever reason, employ the smallest dose calculated to be effective. In general a total tumor dose far exceeding 3 000 r. should be avoided, if only because of the potential hazard of post irradiation sarcoma (after a latent interval usually of 5 years or more)

5 In dealing with what appears to be a malignant bone tumor before resorting to radical surgery obtain expert opinion if there is any reasonable doubt in regard to the diagnosis of sarcoma. Apart from any medicolegal liability entailed, it is possible that the lesion is not so serious as you think. Thus osteomyelitis may simulate Ewing's sarcoma on occasion, as may rapidly developing lesions of eosinophilic granuloma. Instances of aneurysmal bone cyst are not infrequently mistaken for aggressive giant-cell tumors and sometimes for osteogenic sarcoma. With reference to lesions held to represent osteogenic sarcoma, one must be particularly careful to make certain that the condition does not represent some other less serious lesion exhibiting active new-bone formation for whatever reason, e.g periosteal ossification, myositis ossificans (in an active stage) ossifying hematoma, or exuberant callus. In the matter of recognizing and treating skeletal lesions in general, it is my impression that more mischief is done currently through overdiagnosis than through failure to recognize malignant tumors promptly

6. If on the other hand, the malignant nature of a bone lesion has been clearly established, treat it without undue delay and as aggressively as may be necessary The result of compromise and temporizing (too little and too late) is usually complete therapeutic failure In dealing with early chondrosarcoma, for example delay may sometimes mean the difference between cure and ultimate fatality This urgency may apply also to instances of central fibrosarcoma and primary reticulum-cell sarcoma which can also be cured if they are appropriately treated before metastasis has developed.

II

General Remarks on Roentgenographic Interpretation of Skeletal Lesions

Despite the impression that still prevails in some quarters, there are no fixed formulas for the roentgen diagnosis of bone tumors, and most of the allegedly pathognomonic signs, while sometimes helpful, are often fallacious. It is true, for example, that a sclerosing tumor in the lower end of a femur which has obviously penetrated the cortex and provoked the formation of perpendicular radiopaque striations within the cuff of tumor tissue beneath the raised periosteum will in all probability prove to be an osteogenic sarcoma. On the other hand, if a radiologist necessarily expects this distinctive appearance as a criterion for diagnosis, he is very likely to miss more than half of all the osteogenic sarcomas that he encounters, because the indications of new bone formation and of periosteal reaction to cortical perforation by tumor are often much more subtle. In fact, there are an appreciable number of osteogenic sarcomas, mainly of osteolytic type, whose roentgen appearance is so equivocal that it is hardly possible to venture any definitive diagnosis prior to biopsy although one may perhaps suspect the presence of a malignant neoplasm. As for the particular sign commonly alluded to, not only is this not constant, as indicated but it is also not actually specific. That is to say the finding of perpendicular striae of periosteal new bone is not in itself an indication necessarily of osteogenic sarcoma, inasmuch as it may be observed on occasion as a reaction to the presence of metastatic carcinoma, Ewing's sarcoma, or even tuberculosis of the shaft of a long bone.

To cite another instance in point, while it is true that an occasional lesion of Ewing's sarcoma may manifest reactive striations of periosteal new bone laid down parallel to the cortex (so-called "onionpeel" effect) most lesions will not present this appearance. Moreover this pattern of periosteal new bone apposition, when present, is not in itself indicative necessarily of Ewing's sarcoma, for it may be observed at times with active osteomyelitis and even in an occasional instance of

osteogenic sarcoma. Actually, the presenting lesion in a case of Ewing's sarcoma which is still in an early stage of its evolution is usually reflected roentgenographically by a vaguely mottled area of rarefaction without any clearly discernible periosteal reaction, so that it may not be readily distinguishable from a focus of osteomyelitis. In a more advanced stage, when the tumor has already broken through the cortex and produced an overlying soft tissue mass, its appearance will readily suggest a malignant neoplasm, although again this picture may not be at all distinctive and at times simulates that of osteogenic sarcoma.

Continuing in the same vein the roentgenographic picture formerly held to characterize giant-cell tumor of bone, namely that of an expanded lesion presenting a trabeculated pattern suggesting an agglomeration of "soap bubbles," is not the picture presented by most instances of (untreated) genuine giant-cell tumor. Actually this allegedly pathognomonic sign is distinctly misleading. Most giant-cell tumors grow too rapidly to provoke the pattern indicated. The latter is much more likely to be encountered with other lesions (e.g., hemangioma, nonosteogenic fibroma, fibrous dysplasia, enchondroma, or chondromyxoid fibroma) which grow more slowly and therefore permit the development of reactive grooves and spurs on the endosteal surface of the attenuated cortex overlying the lesion. More significant in so far as a diagnosis of giant-cell tumor is concerned are the location of the area of rarefaction in the end of the affected limb bone (especially in a patient past the age of 20 years), thinning and expansion of the cortex particularly on one side, and the absence of periosteal new-bone formation over the thinned and expanded cortex. However, as indicated elsewhere, even these features are not infallible guides to the correct diagnosis, and it is important to recognize that on occasion a chondrosarcoma (which does not display telltale calcification), a central fibrosarcoma (which has not as yet broken through the cortex), or even a solitary focus of myeloma may produce a roentgen picture not readily distinguishable, with any degree of assurance at least, from that of giant-cell tumor. It follows as an obvious corollary that one must reserve judgment as to the diagnosis in such cases until an adequate biopsy has been examined. By the same token, the wisdom of the practice of instituting radiation therapy on the strength of a roentgen impression alone, unverified by biopsy, is open to serious criticism.

Still another instance in which an oft repeated radiologic cliché may actually render a disservice relates to the emphasis placed upon the presence of multiple punched-out defects in many bones and particularly the calvarium, as a distinguishing hallmark of multiple myeloma. While no one will deny that some cases of far advanced myeloma present this picture, it is essential to bear in mind that others present merely vaguely defined rarefactions in a number of bones and that still others show widespread osteoporosis without any obvious localized defects (reflecting diffuse infiltration of the bone marrow by myeloma). Furthermore, as is now generally recognized, an appreciable number of cases of myeloma present a single sizable localized area of rarefaction (in the vertebral column, an innominate bone or a long bone, for example) as their initial manifestation, without any demonstrable roentgen evidence of involvement of the remainder of the skeleton. As for the calvarium in particular, this may fail to show out[illegible] involvement even

in well-established cases of myeloma in which clear-cut defects are obvious in other bones. Moreover the presence of multiple osteolytic defects in the skull is not in itself an indication necessarily of multiple myeloma, inasmuch as comparable defects may be observed occasionally with metastatic carcinoma.

The foregoing comment is not intended to detract from the great value of the roentgenographic findings as an indispensable clue to the diagnosis of tumors and tumorlike lesions of bone. On the contrary it is intended to emphasize the necessity for objective interpretation rather than to place undue reliance upon outdated criteria which were not predicated upon sound pathologic correlation. As a basis for diagnosis, one must think in terms of the actual pathologic lesion at hand, its topography and location, its apparent rate of growth, and what it has done to the bone, and any attempt to operate in a world of shadows divorced from pathologic reality is fraught with hazard. It is of considerable value, incidentally, in sharpening one's diagnostic acumen to follow through by examining actual specimens obtained at surgery or autopsy and taking roentgenograms of these specimens and also of specimen slices as indicated for comparison with the clinical films.

In the interest also of an objective approach to problems in diagnosis, I wish to emphasize the importance of the use of precise language in describing the roentgen appearance of bone lesions in general, as essential to clear thinking about them. For example, a circumscribed area of rarefaction is not necessarily a cyst, although it is often loosely designated as such. To be sure, such a lesion may actually contain fluid, but more often it is found on surgical exploration to be solidly filled with fibrous tissue, tumor cartilage, or some other type of tumor tissue. To cite another instance in point, certain lesions are often described as trabeculated, implying that they are traversed by osseous septa, when actually the effect observed reflects the projection on a flat plate of irregularities on the inner contour of the shell of bone delimiting the lesion peripherally

It is essential also to bear in mind that roentgenographic interpretation has its inherent limitations, and that not infrequently even a skilled observer possessed of the essential clinical data must be content to record a tentative impression subject to verification by biopsy or to suggest two or more plausible alternate possibilities. To cite a pertinent instance, an equivocal lesion in the upper shaft of a humerus of a child or a young adult may conceivably represent a focus of fibrous dysplasia or an enchondroma (devoid of telltale calcific stippling) or a latent bone cyst which has moved away from the epiphyseal plate region. In such an instance it may be quite difficult prior to surgical exploration to forecast the precise nature of the lesion and one does not lose face by declining to go out on a limb

Many advances have been made in the field of skeletal pathology in recent years and, specifically many new lesions, both neoplastic and non-neoplastic, have been clearly delineated as clinical and pathologic entities. These new concepts must be gradually assimilated and, self-evident though this may seem, one must keep an open mind in regard to them. The dogmatism of a few radiologists which says, in effect, that if you disagree with me you must be wrong hardly seems

justified or conducive to progress. Because a radiologist, or a surgeon for that matter has not had the good fortune, for example, to encounter a bona fide osteoid-osteoma in his personal experience it does not follow at all that the lesion is mythical and hence to be ignored, or that every lesion which resembles an osteoid-osteoma developing in relation to the cortex of the shaft of a long bone is necessarily a cortical bone abscess.

Finally it is of the utmost importance to stress the basic principle that roentgen impressions of skeletal lesions should be verified by tissue examination before one proceeds with definitive treatment, whatever that may be. As indicated I am strongly opposed to blind irradiation, except perhaps for palliation of an obviously advanced malignant neoplasm in an inaccessible site. If an open biopsy or surgical treatment is not contemplated for whatever reason, then at least one should resort to needle aspiration biopsy whenever possible, in the hope (though not necessarily the expectation) that it may yield information of diagnostic value. As has already been noted for example, a lesion in the lower end of a femur whose x ray picture seems clearly to resemble that of a giant-cell tumor may on occasion prove to be a sarcoma requiring prompt ablation rather than irradiation. By the same token, I am categorically opposed to radical surgery undertaken on the strength of a roentgen diagnosis alone, however well founded it may seem. In that connection, I recall the pertinent instance of a tumor in the upper end of a humerus presenting all the roentgenographic features held to characterize osteogenic sarcoma, which proved on biopsy to represent a focus of metastatic carcinoma. It is a relatively simple matter in such cases to obtain a small bit of tumor tissue to confirm the clinical impression

III

Classification of Primary Tumors of Bone

It appears logical to preface any treatise on tumors developing within bone with a classification for as Ewing has aptly stated unless the surgeon or the pathologist is familiar with what *may* happen in bone, he is hardly able to recognize what *has* happened It is true that a number of such classifications have already been advanced including that prepared by Ewing in 1939 for the Bone Sarcoma Registry of the American College of Surgeons, but their usefulness is marred by pathologic inaccuracies, lack of completeness, or undue preoccupation with minor subdivisions of dubious significance and with theoretical considerations of histogenesis. I, therefore feel justified in venturing my own listing of primary tumors appearing within bone as a structure and involving at one time or another not only the osseous tissue proper and the bone marrow but also the supporting connective tissue along with its component nerves blood vessels and fat.

This classification (Table I) reflecting current concepts provides within its framework a place for all known primary neoplasms of bone including those recently delineated as pathologic entities, with the exception only of the odontogenic tumors and the comparatively uncommon tumors arising from the periosteum, whose biologic behavior sets them apart as a group unto themselves (Chapter 24) It includes the benign as well as the malignant primary tumors. An attempt has been made also to indicate the malignant counterpart (if any) of each of the benign tumors listed and, after the manner of a periodic table, to reserve a place for such specific malignant tumors as may be hitherto unrecorded, in the event that they are observed and recognized in the future. Except for this provision, the scheme has been made as streamlined as possible in the interest of clarity and conciseness, and lists only neoplastic entities that have been described as such or that can be readily identified on pathologic examination, if one is familiar with them. To be sure it reflects my personal views, and in some few debatable instances (e.g., Ewing's sarcoma of bone) necessarily entails arbitrary decisions as to histogenetic origin. Be that as it may this classification is presented for consideration as a helpful working hypothesis along with pertinent comment in support of the proposed

Table I

Origin		Benign Tumors of Bone	Malignant Counterpart (if any)	Malignant Tumors of Bone (arising through malignant change or independently)
Of cartilage cell or cartilage forming connective tissue derivation	Peripheral	Osteocartilagenous exostosis (multiple exostosis)	Peripheral chondrosarcoma	Chondrosarcoma
	Central	Enchondroma (skeletal enchondromatosis)	Central chondrosarcoma	
		Benign chondroblastoma	(Not known)	
		Chondromyxoid fibroma	(Not known)	
		Other chondroid tumors		
Of osteoblastic derivation		Osteoma	(Not known)	Osteogenic sarcoma
		Osteoid-osteoma	(Not known)	
		Benign osteoblastoma	(Osteogenic sarcoma)	
Of nonosteoblastic connective-tissue derivation		Nonosteogenic fibroma	(Not known)	Fibrosarcoma
		Least-aggressive giant-cell tumors →	More aggressive & malignant giant-cell tumors →	Frankly malignant giant-cell tumors
Of mesenchymal connective tissue origin		———		Ewing's sarcoma
Of hematopoietic origin		———		Multiple myeloma
				Chronic myeloid leukemia
				Acute leukemias
				Malignant lymphoma: Reticulum-cell sarcoma; "Lymphosarcoma; Hodgkin's disease
Of nerve origin		Neurofibroma	(Malignant schwannoma)	
		Neurilemoma		
Of vascular origin		Hemangioma	(Hemangioendothelioma)	Hemangioendothelioma
		Hemangiopericytoma (glomus)		
Of fat-cell origin		Lipoma		Liposarcoma
Of notochordal derivation		———		Chordoma
Of adamantine or possibly basal-cell derivation		———		So-called adamantinoma

categories. In this book, it will serve as a framework of reference for the various benign and malignant primary neoplasms of bone which will be discussed in the chapters that follow

Tumors of Cartilage-Cell or Cartilage Forming Connective Tissue Derivation

As indicated, the tumors which are composed of frank cartilage or which appear to be derived from cartilage forming connective tissue are bracketed in this group. A significant distinction is maintained between those which develop peripherally as cartilage-capped exostoses (osteocartilaginous exostosis or osteochondroma) and those which develop centrally within the interior of the affected bone. The tendency manifested in the recent French and Italian literature, particularly, to lump together the osteocartilaginous exostoses and the enchondromas as related expressions of a vague category of so-called "osteogenic disease" is strongly to be deprecated as seeking to obliterate well-established and useful distinctions.

In regard to *osteocartilaginous exostoses* which, as is well known, may be solitary or multiple (hereditary multiple exostosis[17]) one can maintain with some cogency that they actually represent an expression of a skeletal developmental anomaly While that is true, they are undoubtedly tumors in a clinical sense and, moreover in the case of multiple exostoses at least, they not infrequently give rise to chondrosarcoma through activated growth of their cartilage caps. Incidentally, such peripheral chondrosarcomas are sometimes mislabeled as instances of osteogenic sarcoma, owing to the fact that the older portion of the tumor particularly is likely to be rather heavily calcified and ossified

The most frequently encountered benign central cartilage tumor is the common *enchondroma*[21] which is composed of facets of mature hyaline cartilage. Occasionally especially when it is situated within a long bone, it may undergo malignant change and insidious conversion to central chondrosarcoma.[23] As is well known also enchondromas may be multiple (skeletal enchondromatosis) and at times exhibit a tendency to monomelic or predominantly unilateral distribution (Ollier's disease) In such cases, the tendency to malignant transformation is rather strong, and the development of chondrosarcoma in some one, or even two or more cartilage foci simultaneously is not unusual. On the other hand, one may of course encounter instances of fully evolved central chondrosarcoma in which there is no evidence to indicate that the neoplasm developed on the basis of a pre-existing enchondroma.

Also included in this group is the tumor formerly regarded as the calcifying or chondromatous variant of giant-cell tumor which Jaffe and I[19] have designated as *benign chondroblastoma of bone* Its recognition is of some practical importance, inasmuch as instances of it are not infrequently overdiagnosed as chondrosarcoma or even osteogenic sarcoma, with the attendant recommendation of ablation. The distinctive pathologic and clinical features that set it apart from genuine giant-cell tumors and justify its inclusion among the bone tumors derived from cartilage forming connective tissue have been emphasized elsewhere.[21] For the reasons indicated, and also because the capital epiphysis of the humerus is one of its less common sites of origin, the eponym of Codman's tumor is avoided. This peculiar neoplasm responds satisfactorily to thorough curettement and I have not observed

Table I

	BENIGN TUMORS OF BONE	MALIGNANT COUNTERPART (IF ANY)	MALIGNANT TUMORS OF BONE (ARISING THROUGH MALIGNANT CHANGE OR INDEPENDENTLY)
OF CARTILAGE CELL OR CARTILAGE FORMING CONNECTIVE TISSUE DERIVATION — PERIPHERAL	OSTEOCARTILAGENOUS EXOSTOSIS (MULTIPLE EXOSTOSIS)	PERIPHERAL CHONDROSARCOMA	CHONDROSARCOMA
OF CARTILAGE CELL OR CARTILAGE FORMING CONNECTIVE TISSUE DERIVATION — CENTRAL	ENCHONDROMA (SKELETAL ENCHONDROMATOSIS)	CENTRAL CHONDROSARCOMA	CHONDROSARCOMA
	BENIGN CHONDROBLASTOMA	(NOT KNOWN)	
	CHONDROMYXOID FIBROMA	(NOT KNOWN)	
	OTHER CHONDROID TUMORS		
OF OSTEOBLASTIC DERIVATION	OSTEOMA	(NOT KNOWN)	OSTEOGENIC SARCOMA
	OSTEOID-OSTEOMA	(NOT KNOWN)	
	BENIGN OSTEOBLASTOMA	(OSTEOGENIC SARCOMA)	
OF NONOSTEOBLASTIC CONNECTIVE TISSUE DERIVATION	NONOSTEOGENIC FIBROMA	(NOT KNOWN)	FIBROSARCOMA
	LEAST-AGGRESSIVE GIANT-CELL TUMORS →	MORE AGGRESSIVE & MALIGNANT GIANT-CELL TUMORS →	FRANKLY MALIGNANT GIANT-CELL TUMORS
OF MESENCHYMAL CONNECTIVE-TISSUE ORIGIN	—		EWING'S SARCOMA
OF HEMATOPOIETIC ORIGIN	—		MULTIPLE MYELOMA
			CHRONIC MYELOID LEUKEMIA
			ACUTE LEUKEMIAS
			MALIGNANT LYMPHOMA: RETICULUM-CELL SARCOMA, "LYMPHOSARCOMA", HODGKIN'S DISEASE
OF NERVE ORIGIN	NEUROFIBROMA	(MALIGNANT SCHWANNOMA)	
	NEURILEMOMA		
OF VASCULAR ORIGIN	HEMANGIOMA	(HEMANGIOENDOTHELIOMA)	HEMANGIOENDOTHELIOMA
	HEMANGIOPERICYTOMA (GLOMUS)		
OF FAT-CELL ORIGIN	LIPOMA		LIPOSARCOMA
OF NOTOCHORDAL DERIVATION	—		CHORDOMA
OF ADAMANTINE OR POSSIBLY BASAL-CELL DERIVATION	—		SO-CALLED ADAMANTINOMA

categories. In this book it will serve as a framework of reference for the various benign and malignant primary neoplasms of bone which will be discussed in the chapters that follow.

Tumors of Cartilage-Cell or Cartilage-Forming Connective Tissue Derivation

As indicated, the tumors which are composed of frank cartilage or which appear to be derived from cartilage forming connective tissue are bracketed in this group. A significant distinction is maintained between those which develop peripherally as cartilage-capped exostoses (osteocartilaginous exostosis or osteochondroma) and those which develop centrally within the interior of the affected bone. The tendency manifested in the recent French and Italian literature, particularly, to lump together the osteocartilaginous exostoses and the enchondromas as related expressions of a vague category of so-called "osteogenic disease" is strongly to be deprecated as seeking to obliterate well-established and useful distinctions.

In regard to *osteocartilaginous exostoses*, which, as is well known, may be solitary or multiple (hereditary multiple exostosis[17]), one can maintain with some cogency that they actually represent an expression of a skeletal developmental anomaly. While that is true, they are undoubtedly tumors in a clinical sense and, moreover, in the case of multiple exostoses at least, they not infrequently give rise to chondrosarcoma through activated growth of their cartilage caps. Incidentally, such peripheral chondrosarcomas are sometimes mislabeled as instances of osteogenic sarcoma, owing to the fact that the older portion of the tumor particularly is likely to be rather heavily calcified and ossified.

The most frequently encountered benign central cartilage tumor is the common *enchondroma*,[21] which is composed of facets of mature hyaline cartilage. Occasionally, especially when it is situated within a long bone, it may undergo malignant change and insidious conversion to central chondrosarcoma.[20] As is well known also, enchondromas may be multiple (skeletal enchondromatosis) and at times exhibit a tendency to monomelic or predominantly unilateral distribution (Ollier's disease). In such cases, the tendency to malignant transformation is rather strong, and the development of chondrosarcoma in some one, or even two or more cartilage foci simultaneously is not unusual. On the other hand, one may of course encounter instances of fully evolved central chondrosarcoma in which there is no evidence to indicate that the neoplasm developed on the basis of a pre-existing enchondroma.

Also included in this group is the tumor formerly regarded as the calcifying or chondromatous variant of giant-cell tumor, which Jaffe and I[19] have designated as *benign chondroblastoma of bone*. Its recognition is of some practical importance, inasmuch as instances of it are not infrequently overdiagnosed as chondrosarcoma or even osteogenic sarcoma, with the attendant recommendation of ablation. The distinctive pathologic and clinical features that set it apart from genuine giant-cell tumors and justify its inclusion among the bone tumors derived from cartilage-forming connective tissue have been emphasized elsewhere.[21] For the reasons indicated, and also because the capital epiphysis of the humerus is one of its less common sites of origin, the eponym of Codman's tumor is avoided. This peculiar neoplasm responds satisfactorily to thorough curettement and I have not observed

any instances of aggressiveness or spontaneous malignant change nor have any such instances been recorded in the literature to date.

Still another tumor which seems clearly to belong in this category though not composed of full fledged hyaline cartilage, is the distinctive benign tumor which Jaffe and I[11,12] christened *chondromyxoid fibroma of bone* in 1948 This tumor also is likely to be mistaken for chondrosarcoma or myxosarcoma if one is not familiar with it, although it is apparently entirely benign and does not tend to recur after curettement, even without supplementary irradiation. If the malignant counterpart of this neoplasm exists, it has not been observed to date or, at least, recognized as such. As indicated elsewhere, the tumor is usually encountered in a bone of a lower limb although instances of it have been observed in other sites. It has been interpreted as a peculiarly differentiated connective tissue tumor exhibiting, in the course of its evolution, certain chondroid and also myxoid traits which hallmark the lesion cytologically

The provisional category of chondroid tumors other than benign chondroblastoma and chondromyxoid fibroma has reference to certain atypical tumors composed of cartilage forming connective tissue that is only partially differentiated. Some of these are reminiscent of benign chondroblastoma (although they may occur in atypical sites and in older patients) others bear some resemblance cytologically to chondromyxoid fibroma and still others appear to be differentiating in both directions simultaneously In addition there are occasional tumors composed of more primitive spindle connective tissue cells (precartilage mesenchyme?) forming only a few small patches of chondroid matrix to reveal their nature. Altogether I have observed material from 15 such tumors to date, the great majority of which developed in bones of the foot. Although their microscopic appearance is calculated at times to arouse a suspicion of malignancy their clinical behavior has not been aggressive.

It is pertinent at this point to comment briefly upon the question of the existence of primary tumors which may be appropriately designated as myxoma or myxosarcoma of bone, and to indicate why no provision has been made for categorizing such tumors in the proposed classification. It is true that Bloodgood reported a number of tumors under this head (1924) but his pathologic data afford only the vaguest indication of what he may actually have been dealing with. One of his illustrated cases may conceivably have represented an instance of chondromyxoid fibroma of bone, while some others which had more serious consequences may well have been chondrosarcomas. It is well known that chondrosarcomas, especially the larger ones, may undergo degeneration and cystic softening in places, and that such areas may present a myxoid appearance histologically This tendency apparently accounts for the listing in Ewing's classification of myxosarcoma" as a subgroup in the "chondroma series." I see no valid reason to so dignify a minor secondary feature which does not alter the clinical behavior of the tumor or its basic character and for the same reason, I abjure such confusing combination names as chondromyxosarcoma. In dealing with osteogenic sarcoma also, one may occasionally observe fields of malignant myxoid connective tissue, especially at the periphery although not in the more representative central portion of the neoplasm.

The designation of "myxoma" has also been applied to certain tumorlike, myxoid connective tissue lesions in jaw bones particularly although some of these lesions, at least, may be plausibly regarded as peculiar modified foci of fibrous dysplasia. It should be noted also that Stout in his A F I P fascicle on tumors of the soft tissues makes mention in passing (F-79) of myxomas in bones "where curettage has sometimes resulted in lasting cures," but without further details it is difficult to surmise precisely what he is referring to. As for the tumor reported as "myxoma of bone" by Bauer and Harrell (1954), this seems clearly to represent an instance of chondromyxoid fibroma. Altogether I have never encountered a skeletal neoplasm which warranted the designation of pure myxoma or myxosarcoma of bone.

Tumors of Osteoblastic Connective Tissue Derivation

The name *osteoma* is a much abused one which is often employed to characterize a miscellaneous group of lesions, some of which are not even neoplastic. Thus, it has been used loosely to denote burned-out osteochondromas in which the cartilage cap has involuted, bony spurs induced by trauma or inflammatory reaction, the condition of hyperostosis frontalis interna, as well as certain lesions of fibrous dysplasia developing in the facial and jaw bones particularly. Further, the eburnated, localized, single or multiple hyperostoses that one occasionally observes on the calvarium have also been called osteomas. These are generally fully evolved bony protuberances by the time one has occasion to examine them, and there is no way of telling at this stage whether they had their origin in neoplastic osteoblastic activity. In this classification in keeping with current usage the term "osteoma" is restricted specifically to the designation of certain bony growths of appreciable size, which arise particularly in the bones of the skull preformed in membrane, and are rather prone to extend into the orbit or into one or another of the paranasal sinuses. On rare occasions, one may observe comparable tumors in other bones as well. Cytologically these growths are composed essentially of osteoblastic connective tissue, forming abundant osteoid and new bone, which may eventually become rather compact.

Osteoid-osteoma is now widely accepted as a distinct entity although some observers apparently still are not certain that the lesion represents a genuine neoplasm. Jaffe and I[18, 22] have already stated the reasons for interpreting this lesion as a peculiar benign tumor rather than the result of infection or some other non neoplastic reparative process, and nothing would be gained by reiterating them here. It is true that the incipient phase of the lesion requires further elucidation, and that in some early cortical lesions, particularly one may still observe a residual focus of peculiarly condensed and reconstructed original bone undergoing invasion and resorption by osteoblastic connective tissue. When fully evolved, this nidus is composed essentially of a highly vascularized substratum of osteogenic connective tissue which is actively depositing osteoid matrix and trabeculae of atypical new bone. This can be plausibly interpreted as a neoformation despite its relatively small size as a rule.

Benign osteoblastoma is a category which includes certain osteoid and bone forming tumors, other than osteoma, so-called, and classical osteoid-osteoma. These

benign osteoblastic tumors include the ones previously called osteogenic fibroma by me, as well as those referred to provisionally as "other osteoid tissue forming tumors" in my classification of primary tumors of bone. I have come to believe that there is no fundamental difference between these two subgroups and that for all practical purposes they comprise a single group of benign osteoid forming and bone-forming tumors, which may be appropriately designated as benign osteoblastoma. Their recognition is of practical importance in that they may be mistaken for giant-cell tumor though without sound justification, or for osteogenic sarcoma and as such be treated more aggressively than their benign nature requires.

Tumors of Non-Osteoblastic Connective Tissue Derivation

The rather common benign connective tissue tumor designated as *non-osteogenic fibroma*[38] is one that was delineated in 1942, although occasional instances of it are still mislabeled as giant-cell tumor solitary xanthogranuloma, and fibrous dysplasia, or overdiagnosed by pathologists as osteolytic sarcoma. As the name implies, the lesion is interpreted as a benign neoplasm derived from mature marrow connective tissue which exhibits no tendency to bone formation. The lesion should not be confused with the rather common, small cystlike rarefied (growth) defects in the metaphyses of long bones in children which tend to disappear under observation. It represents a clear-cut clinical and pathologic entity easily recognized roentgenographically in most instances, and readily identified by tissue examination. Cytologically it presents a distinctive pattern of whorled bundles of spindle-shaped connective tissue cells interspersed among which there are occasional small compressed multinuclear giant cells. In some pertinent lesions, though by no means all, areas containing foam-cell aggregates may make their appearance, apparently as a secondary feature.

The propriety of listing *giant cell tumor of bone* among the tumors composed of connective tissue cells which are not bone forming is now generally accepted, regardless of what special significance one attaches to the multinuclear cells which hallmark the lesion cytologically I have no serious objection in principle to the name osteoclastoma preferred by British physicians although the designation of giant-cell tumor is so firmly rooted in the American literature that one can never hope to displace it. Be that as it may if one adheres to a strict definition[39, 22] of what should be regarded as giant-cell tumor and strips away all of the alleged variants so-called, then what is left constitutes a formidable neoplasm. It has become increasingly evident that, while giant-cell tumors are not necessarily sarcomas," neither are they all "benign, and that, with respect to potential seriousness, they may run the whole gamut from one extreme to the other There appears to be substantial agreement, among pathologists at least, that, while many giant-cell tumors are successfully treated by thorough curettement or irradiation, some are undoubtedly aggressive and prone to recur and occasional ones behave like frank sarcomas[41] It is my impression as a working hypothesis that given a sizable group of proved giant-cell tumors, approximately one-half are likely to have a favorable outcome if properly treated by whatever method approximately one-third are likely

to prove more aggressive and recur after treatment (and a considerable proportion of these may eventually come to amputation), while the remaining 15 per cent more or less will be frankly malignant and prone to metastasize to the lungs. An occasional giant-cell tumor is found to be malignant on initial tissue examination, but more often one has to reckon with malignant change incidental to one or more local recurrences.

Tumors of Mesenchymal Connective Tissue Origin

By listing Ewing's sarcoma under this heading I[19] take my stand with those who accept this malignant neoplasm as a tumor entity, distinct and apart from primary reticulum-cell sarcoma of bone marrow[36] (though freely conceding, as Willis maintains, that the diagnosis is often applied uncritically to instances of other tumors, especially carcinoma and neuroblastoma metastatic to the skeleton, and malignant lymphoma involving the bone marrow primarily). At the same time, like many pathologists, I no longer accept Ewing's contention that the tumor is of endothelial origin. I am more inclined to the belief that the tumor cells are probably derived from the undifferentiated mesenchymal connective tissue framework of the marrow, and that, in most instances, the neoplasm is of multicentric origin, thus accounting for its grave prognosis despite prompt radical surgery or effective irradiation of the presenting skeletal tumor focus.

Tumors of Hematopoietic Origin

Under this heading there are listed the various neoplasms which are derived from the blood forming cells of the bone marrow. These tend to become more or less systematized and to involve the hematopoietic organs generally, although occasional ones (e.g., certain instances of myeloma[30] and malignant lymphoma[11]) may appear initially within a single bone and apparently remain localized there for some time. These tumors of hematopoietic origin include multiple myeloma, chronic myeloid leukemia, the acute leukemias and the various expressions of malignant lymphoma, namely reticulum-cell sarcoma,[36, 40] lymphoblastic and lymphocytic lymphoma (lympho-sarcoma[11]) and Hodgkin's disease.[18, 30]

Tumors of Nerve Origin

This category provides a place for the very occasional neurofibromas,[43] and neurilemomas (neurinoma, Schwannoma[7, 13, 37]) that have been encountered within bone. These neoplasms are apparently derived from the connective tissue cells or the Schwann cells of nerves which accompany the nutrient blood vessels of bone. While there has been no comprehensive description to date of malignant Schwannomas developing within bone (rather than invading it secondarily), there is no reason a priori why such neoplasms should not arise there occasionally and, hence, a niche has been provided for them. I have refrained from using the designation of neurogenic sarcoma in this connection in keeping with the sharp contention of Stout[42] that there is no sound basis for the supposition that there is a special variety of nerve fibrosarcoma that can be designated a "neurogenic sarcoma."

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Tumors of Vascular Origin

The simple plexiform and cavernous hemangiomas require no particular comment in this connection, except perhaps to point out that they occur rather infrequently in bone. Several instances of glomus tumor arising within bone are now on record[28] although no comparable instances of less highly organized hemangiopericytoma have as yet been recognized as such.[43] As for the malignant neoplasms, a limited number of aggressive and metastasizing hemangio-endotheliomas of bone have been recorded. Apparently none of these developed through malignant change in a previously benign hemangioma of bone in the course of its clinical observation. In the matter of nomenclature, the designation of malignant hemangio-endothelioma is preferred to angiosarcoma or angioblastic sarcoma.

Tumors of Fat-Cell Origin

Although theoretically the development of a lipoma within fatty bone marrow should occasion no great surprise, for some reason or other such tumors are so rare that I have never encountered one. Haas in Dean Lewis *Practice of Surgery* makes casual mention of a few authentic reported cases, but cites no specific references that can be verified However a number of convincing cases with illustrations have been recorded in recent years (Chapter 20) The existence of primary liposarcoma of bone has been questioned,[44] despite the publication of a number of cases interpreted as such,[8, 46] and its inclusion in the classification is therefore provisional and subject to further consideration. On the other hand, the well-documented case reported recently by Dawson appears much more convincing[9]

Tumors of Notochordal Derivation

It is generally accepted that chordoma develops by neoplastic proliferation of notochordal vestiges situated within the nucleus pulposus of intervertebral discs or occasionally within one or more vertebral bodies.

Tumors of Adamantine or Possibly Basal-Cell Derivation

The listing of adamantinoma of jaw bones, especially the mandible entails no nosological problem whatsoever The reservation pertaining to possible basal-cell derivation has reference rather to so-called adamantinoma arising in the tibia, and occasionally in other long bones, such as the ulna and radius. While the resemblance cytologically of certain of these peculiar locally invasive neoplasms to adamantinoma is not denied, there remains the distinct possibility that some of them at least may have their origin in neoplastic proliferation of aberrant epidermoid rests within the more superficial limb bones. Another intriguing suggestion recently advanced is that the tumors in question are really synovial sarcomas in disguise Hicks[18] and Sinclair and Lederer[37]) Still another approach views so-called adamantinomas of limb bones as malignant angioblastomas (Changus and Stewart[5]) Altogether the problem of interpretation of this small but remarkable group of neoplasms is still moot, and for the present one must keep an open mind about it.

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IV

Osteocartilaginous Exostosis (Osteochondroma)

It seems appropriate to begin a discussion of benign tumors of bone with osteocartilaginous exostosis or osteochondroma as it is often designated, since the latter is by far the most common of the benign tumors. It may be encountered on practically any bone pre formed in cartilage but is observed most often on the long limb bones and, particularly their metaphyseal regions. As is well known, the lesion may be solitary or multiple (hereditary multiple exostosis) Since solitary osteochondroma may be regarded as a limited expression or *forme fruste* of hereditary multiple exostosis[2] which represents a systematized anomaly of skeletal development, one may question the propriety of regarding the growth as a genuine neoplasm. However since it is undoubtedly a tumor in the clinical sense and may on occasion give rise to peripheral chondrosarcoma through activated growth of its cartilage cap it appears logical to so classify it.

Whether single or multiple an osteocartilaginous exostosis represents as its name implies, a cartilage-capped bony growth protruding from the surface of the affected bone At the site of the exostosis the cortical bone is defective and the bony mass constituting the bulk of the exostosis merges with the underlying spongiosa. The lesion appears to have its basis essentially in perverted activity *of the periosteum* which tends to form anomalous foci of metaplastic cartilage. These cartilage foci by continued growth and endochondral ossification may give rise to manifest exostoses. It seems not unlikely furthermore as Keith[3] has expounded that defective modeling of the bone (diaphyseal aclasis) contributes to the broadening and blunting of the affected metaphyseal region. This is a feature that one is more likely to observe in cases of multiple exostosis. The present discussion will be concerned *mainly* with the lesion in its solitary form. For detailed consideration of hereditary multiple exostosis the reader is referred to a comprehensive article by Jaffe (1943) dealing with that subject.

Clinical Features

Sex and Age Incidence.—A series of over 200 hospital cases that I have analyzed indicates that there is apparently no significant difference in sex incidence and that, in regard to age incidence, the condition in the great majority of instances manifests itself clinically during adolescence or childhood and occasionally even in infancy Approximately four fifths of the patients operated upon were under 21 years of age.

Clinical Complaints.—The slow growth of the tumor and the lack of serious disability induced by it are reflected in the comparatively long interval that usually elapses between the recognition of the bony protuberance by the patient and the time he seeks surgical treatment, for whatever reason. Occasionally an osteochondroma may become painful as it enlarges, especially on motion of the affected part. Sometimes following trauma, one may observe a fracture through the stalk of an exostosis. In particular osteochondromas springing from the ankle and foot bones may occasion difficulty on walking or wearing shoes. Not infrequently patients become concerned for cosmetic reasons or because of fear of cancer Finally osteocartilaginous exostoses which have become quite large may cause difficulty through pressure on impinged nerves, as in the case illustrated in Fig 5 and in the remarkable instance reported by Gokay and Bucey in which a bulky osteochondroma of the lumbar vertebral column caused symptoms of compression of the cauda equina.

Localization.—Although osteochondromas not infrequently spring from flat bones (rib, scapula, clavicle, iliac bone, or the spinous process of a vertebral body) they are most often encountered, as noted, on the long tubular bones. By far the commonest locations are the lower metaphysis of the femur and the upper metaphysis of the tibia.

Pathologic Observations

An osteocartilaginous exostosis, as indicated, is a sessile or stalked bony protuberance of variable size and contour, jutting from the affected bone. The sessile exostoses may be plateaulike, or roughly hemispherical, or cauliflower-like with a rather knobby surface. The same variation in contour pattern also holds for many of the stalked exostoses with comparatively short stems. On the other hand, some of the more tubular or conical exostoses may present pronged or spiked ends. Equally wide variation prevails as to size, so that one finds exostoses as small as 1 0 cm. and as large as 10 cm. or more in diameter Whatever its size and shape may be, the exostosis is covered by periosteum which adheres closely to the irregular surface contour The periosteal covering is continuous with that of the adjacent cortical bone This rather avascular collagenous connective tissue covering may be delicate but more often it is comparatively thick, as periosteum goes, and attempts to peel it away from the exostosis show it to be composed usually of a number of layers. When this is accomplished, one observes, as a rule, that the surface of the exostosis is capped, in part or altogether by a layer of blue-white hyaline cartilage. In general the younger the patient presenting the exostosis, the more prominent



Fig. 1   Fig 2A   Fig 2B

Fig. 1 —Osteocartilaginous exostosis (osteochondroma) protruding from the lower end of a tibia and gouging out a defect in the contiguous fibula.

Fig 2A —Roentgenogram of another solitary exostosis springing from the upper end of a humerus

Fig 2B —Roentgenogram of an unusual osteochondroma of a phalanx of a finger



Fig 3



Fig 4

Figs. 3 and 4 —Roentgenogram and photograph of an unusual osteocartilaginous exostosis found at surgical exploration to spring from the pedicle of the tenth dorsal vertebra. (Cou of D A S Isaacson, Los Angeles)



Fig 5 —Old calcified and ossified osteochondroma in a man, aged 54 years, who had been aware of its presence for more than 20 years. The growth caused increasing limitation of flexion and eventually paresthesia from stretching of the lateral popliteal nerve. Examination of the specimen showed a persistent cap of calcified cartilage which exhibited no evidence of recent growth.



Fig 6 —*A* and *B* Hereditary multiple exostosis.

will be its cartilage cap, since *the latter tends eventually to involute.* *Section through* a cartilage-capped exostosis perpendicular to its surface reveals further that the thickness of the peripheral cartilage zone usually varies from 1 to 3 mm. and occasionally may be as much as 5 or 6 mm. On the undersurface of this cartilage cap if endochondral ossification is still in progress, one observes a thin, yellowish growth zone or plate, and beneath this spongy bone comprising the bulk of the lesion. The marrow is usually fatty but may be myeloid in places (Fig 8)



Fig 7 — *A* Roentgenogram demonstrating the broadening and blunting of the affected bone ends frequently observed in multiple exostosis. *B* Roentgenogram illustrating the characteristic deformity of the forearm bones in multiple exostosis.

Microscopic examination of the cartilage cap of an *exostosis which is still actively growing* is likely to show foci of proliferating cartilage cells *in its deeper layers* reminiscent of the proliferating zone of articular cartilage. As indicated an osteocartilaginous exostosis grows by endochondral ossification of its proliferating cartilage, after the manner of growth at an epiphyseal cartilage plate Similarly its



Fig. 8.—Osteocartilaginous exostosis (osteochondroma). Photomicrograph showing a portion of its cartilage cap. (×40.)



Fig. 9.—Photograph of the wall and lining of a bursa which developed over an exostosis on the shaft of a femur and which contained numerous calcified chondral bodies.

enlargement ceases when this growth zone becomes closed off by a thin plate of bone. There is also a tendency to gradual resorption of the cartilage cores within the subchondral trabeculae of bone adjacent to the growth zone. In some instances, however, these cartilage cores persist for a long time, if not indefinitely. Occasionally, when the process of resorption and reconstruction in this subchondral zone has been particularly faulty, one observes fibrosed marrow impregnated by calcium detritus, as well as irregularly dispersed fields of heavily calcified cartilage intermingled with bone.

The age at which growth of an exostosis ceases is distinctly variable. In general, however, it coincides roughly with the end of the growth period of the individual and often precedes it by several or many years. Thus, one not infrequently observes cessation of growth in specimens from adolescents or even children. In a young adult, the cap of an exostosis is likely to be composed of quiescent cartilage exhibiting calcification and other regressive changes. In older adults, the cartilage cap tends ultimately to involute and gradually disappear, although remnants of it may persist even into the fourth and fifth decades. These residual cartilage nests, although dormant, apparently retain a latent capacity for reactivated growth, affording an explanation for the occasional development of peripheral chondrosarcoma in later life.

Bursae Developing Over Osteocartilaginous Exostoses.—The development of such bursae is not uncommon, particularly in the case of larger exostoses impinging upon muscles and tendons, and their occurrence has long been recognized (so-called "exostosis bursata"[3]). Such a bursal sac, when present, is likely to be attached around the base of the exostosis. As a rule, it contains mucinous fluid and its lining sometimes comes to resemble synovium. It is not uncommon also to find fibrin rice bodies attached to the lining or lying free within the sac and, occasionally, calcified chondral bodies resembling joint mice are encountered. I have observed a rather unusual specimen of a bursa developing around an exostosis of a femur which contained fully 15 calcified, roentgenographically discernible bodies, ranging in size from 1.0 to 2.5 cm. in greatest dimension (Fig. 9).

Treatment and Prognosis

When an osteocartilaginous exostosis is surgically extirpated, its periosteal covering should also be removed rather than stripped back, since, theoretically at least, it may contain or subsequently re-form the cartilage nidus of a recurrent lesion. In actual practice, however, I observed no local recurrences in a series of some 50 patients who had been operated upon, even though some of the exostoses, at least, had been removed subperiosteally.

Peripheral Chondrosarcoma as a Complication.—As noted, the remnants of the cartilage cap of a solitary exostosis may occasionally, after a latent interval of many years, exhibit a spurt of renewed growth and undergo malignant transformation to chondrosarcoma.[4] In some instances this may follow closely upon an injury to the affected site. The development of chondrosarcoma in such cases

is usually a slow and insidious process requiring many months or even several years for its evolution, and such tumors may attain appreciable size before they are recognized clinically Roentgenographically they characteristically manifest rather heavy calcification and ossification especially in the older portion of the growth, which tends to mask their serious nature. By the same token they may be underdiagnosed as calcifying and ossifying chondromas even by the pathologist on the basis of tissue examination, if proper significance is not attached to the finding of atypical cartilage-cell nuclei in the actively growing peripheral portion of the lesion as an indication of early chondrosarcomatous change.[4] It seems important to emphasize therefore that any osteocartilaginous exostosis in an adult, and occasionally even in a younger patient, which takes on a spurt of growth should be regarded as already a chondrosarcoma, irrespective of how much calcification and ossification it exhibits. As such, it should be widely excised at the time of the initial surgical intervention in order to avoid local recurrence of the neoplasm in bulkier and more aggressive form (Figs. 10 and 11)

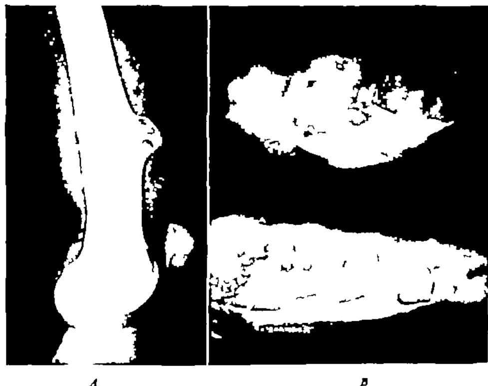


Fig 10—*A* Peripheral chondrosarcoma developing from the cartilage cap of an exostosis on the lower shaft of a femur *B* Roentgenograms of serial slices of the tumor specimen showing more clearly its relation to the exostosis and also focal calcification of the neoplastic cartilage.

When one considers how common solitary osteochondromas are the incidence of chondrosarcoma as a complication appears fortunately to be rather low and probably does not exceed 1 to 2 per cent, judging by our experience One seems hardly justified on that basis alone in advocating the mandatory surgical removal

of all exostoses as a routine preventive measure. On the other hand, one should recommend periodic roentgen examination of exostoses which are not removed, particularly in adults, to make certain that they have remained quiescent. It is important to note, however, that the comparable incidence of chondrosarcoma in cases of multiple exostoses is significantly higher. In this connection, Jaffe has reported the development of chondrosarcoma in 3 of 28 cases of hereditary multiple exostosis (11 per cent) and pointed out that the incidence of malignant change in this same group might ultimately be appreciably higher since the majority of the patients were still young at the time the survey was made.



Fig. 11.—Peripheral chondrosarcoma developing through activated growth of the cartilage cap of an exostosis (apparently solitary) of the upper tibia of a 48-year-old man. The patient had complained of discomfort and gradual enlargement of the affected area for three months. At exploration a fist-sized circumscribed cartilaginous tumor mass was encountered, surrounding a bony projection on the posterolateral surface of the tibia. Roentgenograms, lateral and anteroposterior views.

Summary

Osteocartilaginous exostosis or so-called osteochondroma is by far the most common of the benign tumors of bone. The present survey is based upon a study of more than 200 cases. Although osteochondromas not infrequently spring from flat bones, they are most often encountered on the long tubular bones. The commonest locations are the lower metaphysis of the femur and the upper metaphysis

of the tibia. As its name implies, the lesion represents a cartilage-capped bony growth protruding from the surface of the affected bone. Like the comparable lesions in hereditary multiple exostosis, the solitary exostosis appears also to have its basis in perverted activity of the periosteum which tends to form anomalous foci of metaplastic cartilage. In fact, the weight of evidence lends support to the view that the condition represents a limited or abortive expression of multiple exostosis, the most common of the systematized anomalies of skeletal development. In keeping with this view is the fact that the condition manifests itself clinically in the great majority of instances in adolescence or childhood and occasionally even in infancy.

Osteocartilaginous exostoses exhibit wide variation in size and contour. The development of an overlying bursa is not uncommon and, on occasion, the latter may contain rice bodies or calcified chondral bodies. The exostosis is invested by thickened fibrous periosteum beneath which there is a cap of hyaline cartilage, several millimeters in thickness. The lesion increases in size as a result of endochondral ossification and comes to a standstill when the growth zone is closed off by a thin plate of bone. Subsequently the cartilage cap tends to involute, but remnants of it usually persist which retain a latent capacity for reactivated growth, affording an explanation for the occasional development of peripheral chondrosarcoma in later life. Such chondrosarcomas develop relatively slowly and are not infrequently underdiagnosed as calcifying and ossifying osteochondromas when first observed. The incidence of chondrosarcomatous change in a solitary exostosis is substantially lower than it is in multiple exostosis and hardly seems to warrant mandatory extirpation as a routine preventive measure. When chondrosarcoma does develop, early recognition and wide surgical excision at the initial surgical intervention is of the utmost importance, if one is to obtain a cure.

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V

Solitary Enchondroma of Bone

This discussion deals with the common benign tumor which is composed of facets of mature hyaline cartilage and appears as a single lesion within the interior of some one bone.[3] Most often, it is one of the phalanges, especially of the hand, or a metacarpal bone that is the site of an enchondroma, but not infrequently it is a large limb bone particularly the humerus or femur, and occasionally also the tibia. The innominate bones, too are a frequent site for the development of cartilage tumors, although the latter are usually malignant, i.e. chondrosarcomas,[6] when first recognized Cartilaginous tumors appearing in relation to ribs are almost invariably of the nature of osteocartilaginous exostoses.[4] Central chondromas of ribs and of the sternum are comparatively unusual in my experience, although such cases have been reported The rare occurrence of enchondroma in a patella has likewise been described.[7] So-called enchondromas of the vertebral column have also been noted but some of these, at least, appear actually to represent instances in which herniated intervertebral disc tissue was mistaken for neoplastic cartilage. For practical purposes, therefore, in dealing with solitary enchondroma of bone, one is concerned mainly with pertinent tumors arising within bones of the hand and occasionally of the foot, and within large limb bones. The former are innocuous, as a rule, and the development of chondrosarcoma in a phalanx or in a metacarpal or metatarsal bone is distinctly unusual Enchondromas of long bones, on the other hand, not infrequently undergo malignant change, usually after a comparatively long quiescent interval, and this aspect will be considered presently

Clinical Considerations

Sex and Age Incidence.—There appears to be no predilection for either sex. With respect to age incidence, the great majority of solitary enchondromas are encountered in patients between 10 and 50 years, and their observation in very young children appears to be exceptional.

Clinical History.—From case histories taken as a whole one gains the distinct impression that the tumor develops slowly and insidiously although the clinical complaints may be of relatively short duration. A pertinent instance which



Fig. 12—*A* Enchondroma of proximal phalanx of a finger *B* Roentgenogram of another enchondroma of a middle phalanx of a finger which has appreciably distended and thinned the overlying cortex This particular lesion fails to show any clearly discernible calcific stippling. *C* Photomicrograph of cartilage curetted from enchondroma illustrated in *A* The cartilage-cell nuclei appear uniformly small and inconspicuous. (×200)

may be cited is that of a physician with an enchondroma in the shaft of a femur which had been discovered roentgenographically by chance seventeen years before it began to cause any difficulty The lesion eventually came to surgery only because it became infected. In other instances, an injury to a limb bone, not necessarily a fracture, was responsible for pain, tenderness, and disability and directed attention to a heavily calcified and ossified enchondroma which must have been present for years. A rather common story in instances of phalangeal as well as metacarpal and metatarsal involvement is that the patient was unaware of anything wrong until a local trauma, often slight, was followed by pain and swelling and that a roentgenogram then revealed a rarefied lesion within the affected bone showing pathologic fracture of the attenuated overlying cortex. It is important to point out further that activated growth of an enchondroma may in itself be responsible for pain in the absence of any antecedent injury and these cases in particular must be viewed with suspicion, until biopsy or curettement rules out the possibility of early malignant change.



Fig 13.—Roentgenogram of an old enchondroma in the terminal phalanx of a large toe of a 44-year-old man. Infraction of the attenuated cortex at two points is attributable to a recent injury There had been obvious enlargement of the toe prior to injury however and sections revealed indications of early chondrosarcomatous change. Amputation of the distal phalanx was performed.

Roentgenographic Picture

In phalanges, by far the most common site of localization, an enchondroma appears as a discrete well-circumscribed ovoid rarefaction shadow It is usually located within the shaft of the phalanx at first, and as long as the epiphysis has not yet fused with the shaft, the former is not involved as a rule. Even after fusion

has occurred, the end of the bone is not necessarily invaded Whatever its position, the lesion may be situated centrally and fail to result in expansion of the bone, at least before it has attained appreciable size. More often however, it is located somewhat eccentrically and causes some bulging and thinning of the overlying cortex, which is then prone to fracture These eccentrically placed enchondromas are usually delimited internally by a thin sclerotized line The rarefaction shadow cast by an enchondroma usually has a hazy mottled appearance. It may be vaguely trabeculated, and frequently though not invariably presents dense stippled foci within it, reflecting spotty calcification and ossification.

In metacarpal and metatarsal bones, the roentgenographic changes produced by an enchondroma closely resemble those observed in phalanges. In these bones, however the lesion is likely to be appreciably larger as one might expect, and to result in more prominent bulging of the overlying cortex. Also it seems to favor the distal rather than the proximal part of the shaft of the affected bone.



Fig. 14



Fig. 15

Fig. 14 —Enchondroma in the proximal end of a tibia of a 50-year-old woman. The fuzzy mottling of the lesion reflects focal ossification. The patient had complained of dull pain in the knee region of at least 3 years duration. When the lesion was curetted, it was found to be filled with blue white, somewhat softened cartilage. Despite the clinical suspicion of malignancy sections failed to show any clear-cut indications of chondrosarcomatous change that would justify a recommendation of ablation.

Fig 15 —Roentgenograms of another central cartilage tumor in a tibia (of a 41 year-old man) biopsy sections of which showed evidence of early but definite malignant change justifying amputation The same indications were present in a biopsy specimen obtained one year earlier although their significance was not appreciated at the time.

In the matter of roentgen interpretation, it may be stated in general that a circumscribed, rarefied, and expanded lesion of the character described occurring within a hand or foot bone is exceedingly likely to represent an enchondroma, and if the lesion also exhibits calcific stippling that impression becomes a virtual certainty There is an unfortunate tendency on the part of some surgeons and even radiologists to refer loosely to such rarefied foci as "cysts." It should be noted,

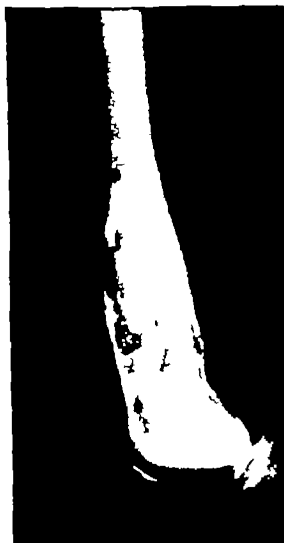


Fig. 16 —Roentgenogram of a relatively early chondrosarcoma in the lower end of a femur developing apparently on the basis of an old calcified and ossified enchondroma. The tumor has induced appreciable widening of the shaft and appears to be penetrating its cortex.

however that genuine fluid filled cysts, if they occur at all in hand bones, must be exceedingly rare and this holds also for genuine giant-cell tumor of bone. It is true that small inclusion cysts lined by squamous epithelium may be encountered occasionally in the distal portion of terminal phalanges of fingers,[1] and that the

lesion of ossifying fibroma has been observed in terminal toe phalanges, but apart from these specific locations the lesions mentioned need hardly enter seriously into the consideration of differential diagnosis.

Much of what has been said concerning the roentgen appearance of enchondroma in hand and foot bones is applicable also to the lesion in long bones. The latter to be sure, is often more extensive and may at times involve a considerable part of the shaft, or even the entire shaft. Also since the overlying cortical bone is relatively dense and thick, it may not be significantly expanded, or if the cortex does bulge slightly its expansion is likely to be limited to a small area. As noted, the presence of spotty or blotchy calcification or even of more delicate calcific stippling within the rarefied focus points definitely to enchondroma. In the absence of telltale calcification and ossification, however the roentgenographic picture may be more ambiguous, and one must then consider as alternate possibilities a solitary focus of fibrous dysplasia, particularly if the lesion has appreciably expanded the affected bone area, and also solitary unicameral bone cyst, especially if the lesion involves the proximal shaft of the humerus. In such instances, only surgical exploration or biopsy will reveal the precise nature of the lesion that is present.

Pathologic Observations

Since a solitary enchondroma is effectively treated by curettement, it is only occasionally that one has the opportunity to examine a tumor intact in its setting One readily gathers however that the adjacent cortical bone is generally attenuated and often reduced to a thin shell if it comes from an area where the cortex has been bulged out, as is commonly the case when the lesion is in a phalanx or a metacarpal or metatarsal bone. On the other hand, when the cortex is not appreciably distended as in the case of a lesion in a large limb bone, one may observe relatively little attenuation of the cortical bone. In any event, the endosteal surface of the cortex in the affected area is likely to show ridges and grooves from gradual erosion by the tumor tissue. There is usually no appreciable periosteal new bone reaction except at sites of infraction of the cortex.

The gross appearance of the neoplastic cartilage obtained by curettement from the interior of the lesion may vary considerably from case to case. Thus, the tissue from a lesion in a finger phalanx often resembles grains of boiled rice. In other instances the lesional tissue consists largely of facets of bluish white hyaline cartilage which is usually firm in consistency but may be comparatively soft and even somewhat myxoid in places. In still others, it consists of bits of dull white cartilage intermingled with yellowish, gritty tissue representing heavily calcified and ossified cartilage On the whole, calcification and ossification in an enchondroma seem best interpreted as an expression of aging or regression, and these changes are likely to be most pronounced in the lesions of long standing in limb bones, although they may also be a prominent feature in some of the older lesions in hand and foot bones. It appears, further that x-ray irradiation tends to induce or accentuate these changes, although in the dosage customarily employed for therapy it will fail to destroy the neoplastic cartilage completely

On microscopic examination of an enchondroma, one observes that the cartilage tumor tissue is divided into facets or lobules of varying size. The connective tissue tracts between the facets of cartilage carry most of the blood vessels in the vicinity of which calcification and ossification of cartilage are usually initiated. Enchondromas also vary considerably with respect to cellularity. Some are rather rich in cells and others are relatively poor, while still others show intermingled richly and poorly cellular areas. The intercellular ground substance is usually hyaline in large part or throughout. The cells within this hyaline matrix tend to lie within lacunae, many of which may be fairly large. A lacuna usually contains a single cartilage cell though some may lodge two, and an occasional one a small nest of cells. In some areas the intercellular matrix may become edematous or even myxoid, in which case the cartilage cells, no longer surrounded by lacunae, tend to be multipolar or stellate in contour. It is the appearance of such modified fields that may cause certain enchondromas to be designated as myxomas or chondromyxomas.

In sections stained with hematoxylin and eosin, the ground substance will often appear dusty, reflecting the presence of calcareous granules within it. When calcification is more extensive, these granules will be rather conspicuous around the lacunae and also at the periphery of the cartilage lobules. Where calcification is particularly heavy, the cartilage cells may be found to have undergone necrobiosis or to have disappeared completely. Further, heavily calcified areas, particularly where they border on the interlobular vascular spaces, tend to undergo osseous metaplasia.

In the cytologic appraisal of the benignity of a central cartilage tumor, one should concentrate wholly on the cartilage cell nuclei, selecting fields which are viable and not too heavily calcified, and remote from any fracture site that may be present. In such fields the cartilage cells of a benign tumor will be found consistently small. Their cytoplasm is generally pale and often more or less vacuolated, and its outlines are frequently indistinct. The cartilage cell nuclei are likewise consistently small and are roundish and dark staining. On scanning many preserved fields from as many parts of the tumor as possible, one may find very occasional cartilage cells which, though small, contain two nuclei, reflecting amitotic division. It should be emphasized, however, that some enchondromas contain practically no cartilage cells with double nuclei, and that even those which do show only a few such cells in occasional fields. In summary, then, the extent of calcification and ossification, the character of the matrix, and the presence and size of the lacunae are of no practical significance. What stamps an enchondroma as benign cytologically is the fact that its viable cartilage cells are uniformly rather small and have single nuclei which are definitely not plump. While one does find, here and there, some cells (still small) with two nuclei, one does not find them regularly in all fields, even in small numbers (Fig. 12, *C*).

As noted, an enchondroma, especially in a long tubular bone, may occasionally undergo malignant transformation. The lesion may have been present as a benign growth for many years and may have been virtually symptomless during that time. Prior to its reviviscence and malignant transformation, the enchondroma may even have become extensively calcified and ossified. The evolution of such a chondrosarcoma, though sometimes rapid, is usually a rather slow and insidious process.

In this connection it should be noted that the onset of persistent pain and spontaneous cortical perforation are ominous signs pointing to significant reactivated growth. Cytologic evidences of change in the direction of malignancy are detectable relatively early but these are often rather subtle at first and present only in certain fields of the tumor To recognize them, one has to have clearly in mind the characteristic cytologic pattern of the benign enchondroma as a standard and be on the alert for significant deviations from this pattern If one finds, even in occasional areas, microscopic fields showing several or many binuclear cartilage cells, many cartilage cells with plump nuclei, and especially any cartilage cells, containing distinctly large or multiple nuclei the tumor should no longer be regarded as a benign enchondroma. Eventually the histologic picture of such a tumor will become that of an obvious chondrosarcoma, but by that time the opportunity of obtaining a cure by radical surgery may have been lost. For pertinent case records emphasizing this important point, the reader is referred to Chapter 14 dealing with chondrosarcoma of bone.

Treatment and Prognosis

Inasmuch as irradiation is not calculated to destroy cartilage tumors effectively the treatment of choice for enchondroma of bone is surgical This consists specifically of curettement, usually followed by chemical cauterization and in addition, under appropriate circumstances, collapse of the distended part of the cortical wall and introduction of bone chips or insertion of a solid bone graft. Of some 14 phalangeal lesions studied by Jaffe and me,[3] a number were merely curetted, some were curetted and cauterized, and some were curetted and filled with bone chips, with or without previous cauterization. No recurrences were noted in any of these cases, and healing was prompt and uncomplicated in all of them except one in which a course of preoperative irradiation therapy had been given. The precise dosage which was used was not known, but the patient stated that she had received "10 x ray treatments without benefit." Postoperatively in this case, the wound suppurated slightly and a number of the bone chips which had been inserted were sequestrated. One cannot, of course, be certain that this complication was attributable to the preoperative irradiation, although it is well known in general that heavily irradiated lesions in bone which are subsequently operated upon are particularly susceptible to infection.

Of some 6 lesions in metacarpal and metatarsal bones investigated, 5 were likewise treated by currettement, collapse of the cortical wall, and introduction of bone chips or a solid graft. In these cases, too the postoperative course was uniformly favorable and there were no recurrences. The single exception noted was a case in which the entire metacarpal bone was extirpated apparently because the surgeon was impressed by the extensive involvement of this bone, although pathologically the lesion was entirely benign

The same principles of surgical treatment were followed in some 5 of 8 lesions of long tubular bones studied, again with uniformly good end results. Of the 3 remaining, 1 (a femoral lesion) had been treated elsewhere by resection of the lower end of the affected bone. Such treatment is obviously too radical for a solitary benign enchondroma, although the surgeon may have felt that by being drastic

he was forestalling malignant transformation of the lesion. In another instance,[8] biopsy was followed ten months later by resection of the affected upper end of the humerus, since in the interval the lesion was persistently painful and showed roentgen evidence of further growth It is interesting to note that sections of the periphery of this tumor showed evidence of early chondrosarcomatous transformation, although the periosteum had not yet been perforated at any point (Fig 17)

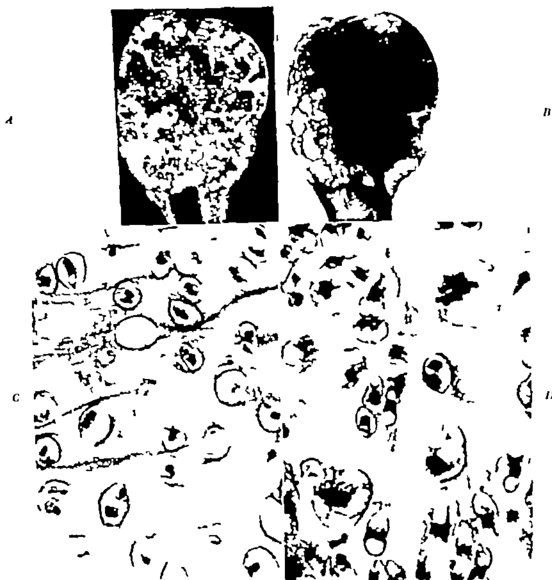


Fig 17—A Photograph of a sagittally sectioned central cartilage tumor in the upper end of a humerus (resected specimen) B Roentgenogram of this specimen reflecting ossification centrally and relative radiolucency at the periphery where the cuff of hyaline cartilage shows little calcification or ossification. C Photomicrograph of biopsy specimen in this case obtained 10 months earlier showing no indication whatsoever of malignant change. D Photomicrograph of neoplastic cartilage from the periphery of the resected specimen illustrated in A clearly indicative of malignant change even though the tumor is still confined by the expanded cortex. Compare with field in C which is also taken at 250 magnifications.

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he was forestalling malignant transformation of the lesion In another instance,[6] biopsy was followed ten months later by resection of the affected upper end of the humerus, since in the interval the lesion was persistently painful and showed roentgen evidence of further growth It is interesting to note that sections of the periphery of this tumor showed evidence of early chondrosarcomatous transformation, although the periosteum had not yet been perforated at any point (Fig 17)



Fig 17—*A* Photograph of a sagittally sectioned central cartilage tumor in the upper end of a humerus (resected specimen) *B* Roentgenogram of this specimen reflecting ossification centrally and relative radiolucency at the periphery where the cuff of hyaline cartilage shows little calcification or ossification. *C* Photomicrograph of biopsy specimen in this case obtained 10 months earlier showing no indication whatsoever of malignant change. *D* Photomicrograph of neoplastic cartilage from the periphery of the resected specimen illustrated in *A* clearly indicative of malignant change even though the tumor is still confined by the expanded cortex. Compare with field in *C* which is also taken at 250 magnifications.

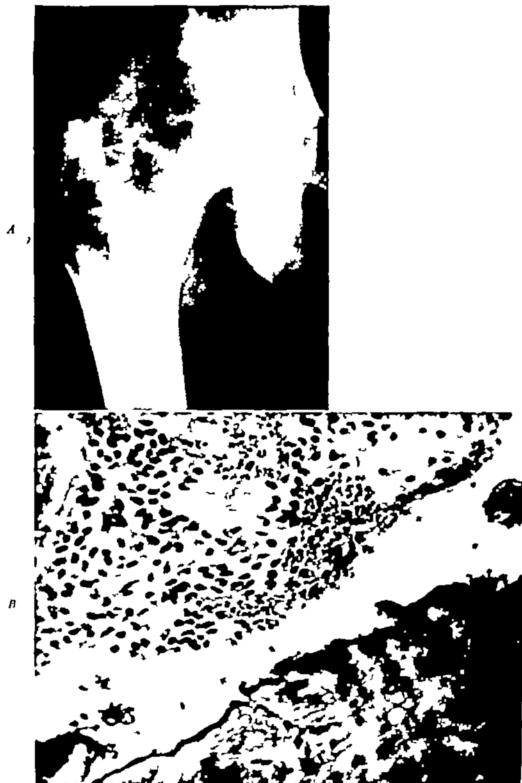


Fig. 18–4. Roentgenogram of a central cartilage tumor situated in the neck and intertrochanteric region of a femur (of a 20-year old woman). The neoplasm has resulted in thinning and erosion of the cortex superiorly. From the roentgen picture alone it is hardly possible to venture the correct diagnosis with any assurance. *B*, Photomicrograph of a selected biopsy field showing (in its upper half) a focus of neoplastic cartilage in which the cartilage cell nuclei are significantly enlarged and compacted. The finding of even an occasional field such as this suffices *to establish a diagnosis of early chondrosarcoma. A 6 year cure was obtained*[5] *without sacrificing* the extremity through resection of the upper femur, replacement of the autoclaved specimen as a graft, and fusion of the hip with the aid of massive tibial grafts. (×200.)

Skeletal Enchondromatosis

One occasionally encounters patients who present central cartilage tumors in multiple sites, and this condition is usually designated as skeletal enchondromatosis, being of the nature of a systematized developmental anomaly Its clinical manifestations often appear early in childhood and the skeletal lesions are sometimes associated with multiple hemangiomas of the skin (so-called Maffuci's syndrome) Depending upon the severity of the condition, the enchondromas may be confined to the bones of a single digit, to several or all of the digits of one or both hands,

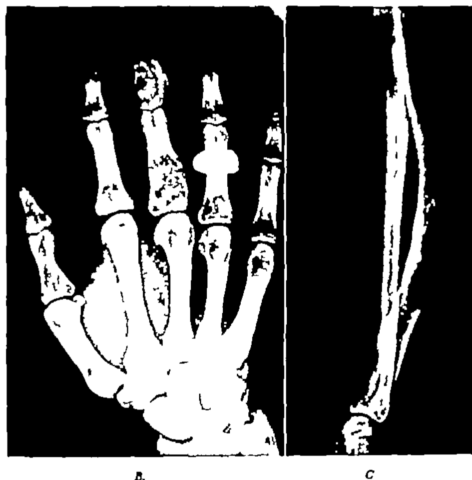


A

Fig 19—A C A Photomicrograph of a representative field from an enchondroma of a tibia (biopsy specimen) in the case of a child with skeletal enchondromatosis (Ollier's disease) who also presented comparable lesions in the femur on the same side, resulting in deformity and appreciable shortening of the affected lower limb The cartilage cells are more numerous than they are ordinarily in a solitary enchondroma, but their nuclei are not enlarged or otherwise significantly altered. (×65)

to the bones of a single limb usually a lower limb or if more extensive may involve many bones in both upper and lower limbs. Even in the cases exhibiting widespread skeletal involvement, there is a strong tendency to unilateral or predominantly unilateral distribution, and these are often referred to as instances of Ollier's disease. The latter eponym incidentally is often misapplied to instances of other conditions, particularly multiple exostosis.

Be that as it may the important consideration to bear in mind in regard to skeletal enchondromatosis is that the individual lesions as compared with solitary enchondromas, appear more cellular histologically exhibit a greater growth potential, and not infrequently exhibit a spurt of growth indicative of malignant change during adolescence or early adult life. When one has occasion to examine amputated limbs from such patients, it is not unusual to find evidence of chondrosarcomatous change



B. C

Fig 19 (cont d) —B Roentgenogram from a case of enchondromatosis limited to the proximal and middle phalanges of the third finger of a hand. C Another instance of limited Ollier's disease in olving the radius, which is bowed (as well as some of the bones of the corresponding hand)

developing in two or more tumor sites simultaneously While the experience of any single observer is scarcely extensive enough to have statistical validity one gains the distinct impression that the hazard of chondrosarcoma in patients with skeletal enchondromatosis, even of moderate extent, is sufficiently great so that one has constantly to be on the alert for it. The grotesque pictures (in the older

literature) of patients with enchondromatosis exhibiting large protruding cartilage tumor masses on the hands and feet and occasionally in other sites also furnish a convincing demonstration of the spontaneous tendency to malignant change in this remarkable condition



Fig 20



Fig 21

Fig 20.—Skeletal enchondromatosis (Ollier's disease) in a child, involving the lower femur and upper tibia and fibula.

Fig 21 —Skeletal enchondromatosis involving the large limb bones of both lower extremities in a child.

It may be pertinent to emphasize that one must clearly distinguish such instances of skeletal enchondromatosis from multiple exostosis, just as one distinguishes a solitary enchondroma from an osteochondroma. In this connection, one must be aware that an enchondroma which has attenuated and has distended its overlying cortex may be mistaken by some for an exostosis and conversely an exostosis whose projection happens to overlap that of the shaft of the affected bone may simulate an enchondroma if only one roentgen view is examined. This consideration may perhaps account for the impression adhered to by some casual observers that the two conditions frequently coexist. Actually I have never observed a single instance in which both peripheral and central cartilage tumors were present in the same patient. Nevertheless, certain French and Italian writers in recent years

have advocated lumping skeletal enchondromatosis and multiple exostosis together under the head of "osteogenic disease," whatever that may mean. This tendency deserves to be deprecated, since it represents a backward step blurring sharp and useful clinical distinctions which have a sound basis in pathologic anatomy. By the same token, one must deplore the practice still adhered to by some writers,[3] of indiscriminately bracketing the two conditions under the single head of chondroma or of dyschondroplasia.



Fig 22.—*A*, *B* and *C* Monomelic skeletal enchondromatosis (Ollier's disease) involving the femur, tibia, and three rays of the foot.

Summary

The clinical, roentgenographic, and pathologic aspects of enchondroma of bone have been discussed. As its name implies, the lesion is a benign cartilaginous growth which develops in the interior of the affected bone. It has a predilection for limb bones, particularly the finger phalanges, the metacarpal and metatarsal bones and the humerus and femur

In relation to tubular bones, the lesion starts its development within the shaft and apparently within the metaphyseal region in particular It may in time come to involve a considerable portion of the shaft. It may also extend into the adjacent or nearer epiphysis, though it is not likely to do so until after the epiphysis has fused with the shaft. An enchondroma developing within a large limb bone is not likely to distend the overlying cortex. In a hand or foot bone however it commonly does so, creating a bulge which can be readily detected clinically

The lesion does not appear to be more common in one sex than in the other Although the great majority of the patients are adolescents or younger adults when they present themselves for treatment, the tumor oftentimes seems clearly to be of rather long standing The clinical complaints are generally mild and are usually referable to swelling of the affected part associated with some pain and tenderness. Many enchondromas come to clinical notice only after trauma has induced infraction of the distended cortex.

The roentgenographic picture is a valuable aid in the diagnosis of enchondroma. In dealing with enchondromas in large limb bones, the presence of radiopaque flecks or blotches representing foci of calcification and ossification often enables one to make the correct diagnosis even when the roentgenographic appearance of the lesion is otherwise ambiguous. In regard to pertinent tumors in phalanges and in metacarpal and metatarsal bones, there is a strong likelihood that one is dealing with an enchondroma if a fairly large area of rarefaction associated with thinning and bulging of the overlying cortex is observed This is true even in the absence of spotty calcification, on the basis of the relative commonness of the lesion in these bones.

Enchondromas in hand and foot bones are, with few exceptions, innocuous and respond satisfactorily to conservative surgical treatment. This consists usually of curettement and filling of the defect with bone chips, or insertion of a bone graft if the defect is large enough to warrant it. The benign character of such lesions is reflected cytologically in the fact that the great majority of the cartilage cells have a single nucleus which tends to be distinctly small in relation to the cell as a whole, and that the few cells which are binuclear likewise have small nuclei and are found only in occasional scattered fields.

An enchondroma, especially one in a long tubular bone, may occasionally undergo malignant transformation. Cytologically in the early stages of this transition the lesion will deviate from the benign pattern just outlined in showing scattered fields containing many cartilage cells with plump nuclei, more than an occasional cell with two such nuclei, and even a number of cartilage cells with atypically large multiple nuclei. The prompt recognition of such early chondrosarcomas is of the utmost importance if one is to obtain a cure by radical surgery

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VI

Benign Chondroblastoma of Bone

Benign chondroblastoma is a tumor that was formerly identified as a giant-cell tumor variant so-called, and specifically as the cartilage-containing giant-cell tumor (Kolodny) the calcifying giant cell tumor (Ewing) or the "epiphyseal chondromatous giant cell tumor" (Codman) In 1942, on the basis of a survey of 9 cases of this peculiar tumor of bone, in collaboration with Jaffe,[19] I suggested the name "benign chondroblastoma of bone" as a more appropriate designation, holding that the lesion had no kinship whatsoever to genuine giant-cell tumor and that it should be regarded as a distinctive tumor in its own right, more logically classified among the benign tumors of bone derived from cartilage cells or cartilage forming connective tissue. Since then, I[13] have had occasion to observe many additional cases, all of which have tended to substantiate the essential soundness of this concept. As for the significant clinical features of the tumor under discussion, we called attention particularly to its curious predilection for young patients, especially males whose ages fall within the second decade—an important point of differentiation from genuine giant-cell tumor which is observed only occasionally in patients under the age of 20 years. In recent years, I have observed a few instances of benign chondroblastoma in adults, but these are exceptional. The roentgenographic picture of the tumor was described as that of a well-delimited, fuzzy or mottled, rarefied focus whose appearance and contour considered in conjunction with its epiphyseal location and particularly the age and sex of the patient, might readily lead one familiar with the lesion to suspect the correct diagnosis even before surgery

Like Ewing we were impressed by the regularly observed tendency to focal calcification within the lesional tissue which constitutes a major feature of its cytologic pattern and affords a readily discernible cue to its recognition. Also we observed, as had Codman, that the tumor regularly involves the epiphyseal end of a long bone, although by the time it comes to clinical notice it may already have extended across the epiphyseal cartilage plate into the adjacent metaphyseal region. While Codman emphasized the occurrence of the tumor in the vicinity of the tuberosity of the upper end of the humerus (in keeping with his particular

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VI

Benign Chondroblastoma of Bone

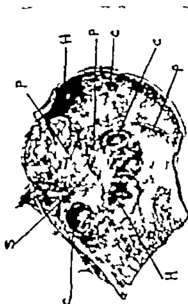
Benign chondroblastoma is a tumor that was formerly identified as a giant-cell tumor variant so-called, and specifically as the cartilage-containing giant-cell tumor (Kolodny), the "calcifying giant cell tumor" (Ewing) or the "epiphyseal chondromatous giant cell tumor" (Codman). In 1942 on the basis of a survey of 9 cases of this peculiar tumor of bone, in collaboration with Jaffe[10] I suggested the name "benign chondroblastoma of bone" as a more appropriate designation, holding that the lesion had no kinship whatsoever to genuine giant-cell tumor and that it should be regarded as a distinctive tumor in its own right, more logically classified among the benign tumors of bone derived from cartilage cells or cartilage forming connective tissue. Since then, I[13] have had occasion to observe many additional cases all of which have tended to substantiate the essential soundness of this concept. As for the significant clinical features of the tumor under discussion, we called attention particularly to its curious predilection for young patients, especially males whose ages fall within the second decade—an important point of differentiation from genuine giant-cell tumor[5] which is observed only occasionally in patients under the age of 20 years. In recent years, I have observed a few instances of benign chondroblastoma in adults, but these are exceptional. The roentgenographic picture of the tumor was described as that of a well-delimited fuzzy or mottled, rarefied focus whose appearance and contour considered in conjunction with its epiphyseal location and particularly the age and sex of the patient, might readily lead one familiar with the lesion to suspect the correct diagnosis, even before surgery.

Like Ewing, we were impressed by the regularly observed tendency to focal calcification within the lesional tissue which constitutes a major feature of its cytologic pattern and affords a readily discernible cue to its recognition. Also we observed as had Codman, that the tumor regularly involves the epiphyseal end of a long bone, although by the time it comes to clinical notice it may already have extended across the epiphyseal cartilage plate into the adjacent metaphyseal region. While Codman emphasized the occurrence of the tumor in the vicinity of the tuberosity of the upper end of the humerus (in keeping with his particular

interest in lesions of the shoulder region) we found that it develops with greater frequency in the lower end of the femur and the upper end of the tibia and appears on occasion in the lower end of the tibia as well. We[13] recently observed a typical lesion which had developed within the capital epiphysis and adjacent neck region of a femur (Fig 26) Thus far I have observed the tumor only in the large tubular limb bones, namely, the femur tibia, and humerus (in that order of frequency) although Coley and Santoro claim to have found it also within hand and foot bones.

In our survey of additional relevant papers, we pointed out that others had also encountered sporadic instances of the tumor but failing to appreciate its special features, had overdiagnosed it as chondrosarcoma (Geschickter and Copeland,[4] Phemister and Hammerström) or even as osteogenic sarcoma (King) If the tumor in question possesses any malignant potentiality whatsoever we have never observed any indication of it, and to our knowledge all of our patients responded satisfactorily to conservative treatment. An occasional case is still reported as a giant-cell tumor and occasional cases are still overrated as sarcoma, especially chondrosarcoma, by pathologists who should know better





A B

Fig 25 — A Roentgenogram of a benign chondroblastoma developing in the upper end of a humerus, the site stressed by Codman. B Photograph (reduced ½) of a coronally sectioned upper end of a humerus showing a pertinent tumor comparable to that illustrated in A It involved the tuberosity and adjacent portions of the capital epiphysis. The letter notations have reference to remnants of the disrupted epiphyseal cartilage plate and to foci of hemorrhage cystic softening and fibrous replacement within tumor tissue. The patient was a boy 16 years of age in whom surgical resection was done on the mistaken premise that the tumor represented a sarcoma.

Clinical Features

Roentgenographic Picture.—Since gross specimens showing an entire tumor intact within its setting are seldom available our knowledge concerning the manner in which the tumor develops, and its effect upon the surrounding bone is largely gleaned from x ray pictures of pertinent lesions. These show that the neoplasm tends to be round or ovoid in contour and, as noted may be confined to part of

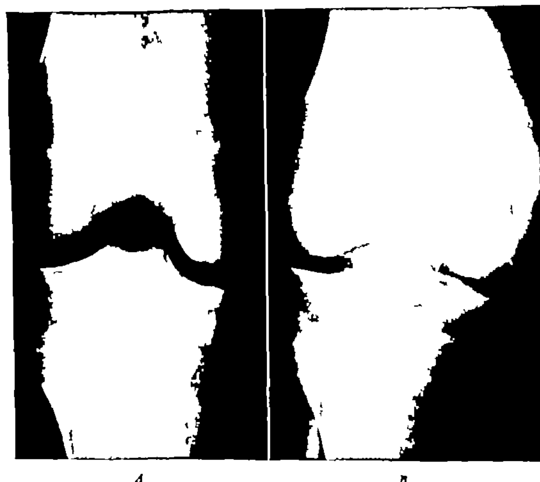


FIG 24—A and B Representative roentgenograms of two benign chondroblastomas situated in the upper epiphysis of the tibia and the lower epiphysis of the femur respectively their most common sites of localization.

an epiphysis, if still relatively small or involve also part of the adjacent metaphysis, having already broken across the epiphyseal cartilage plate. When it involves the metaphysis as well it may sometimes be so eccentrically located as to bulge out the overlying cortex without however destroying it. Actually the tumor may vary in size from a small focus not much larger than an osteoid-osteoma nidus to one measuring as much as 6 cm. in greatest diameter Whatever its size, its

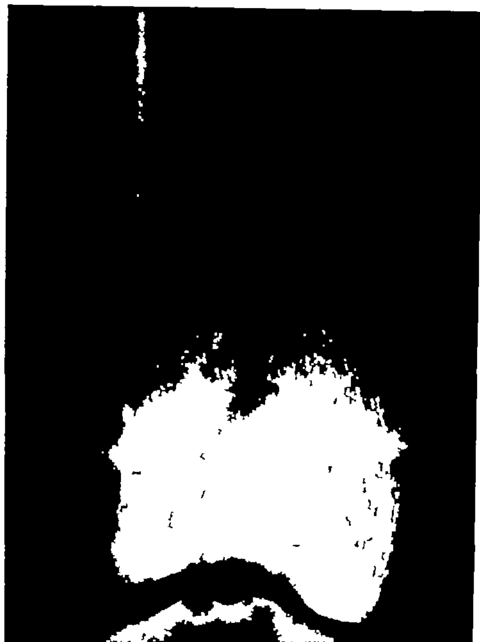


Fig 25—Roentgenogram of another pertinent tumor in a young man 20 years of age originating in the lower epiphysis of a femur and extending into the metaphysis. The tumor has provoked some sclerosis of the surrounding spongy bone. The biopsy sections in this case were overdiagnosed as osteogenic sarcoma and amputation was performed on the basis of this mistaken impression.

roentgenographic appearance is that of a fuzzily mottled, rarefied focus which tends to be delimited by a well-defined, narrow, encircling line of sclerotized bone. The fuzzy mottling of its shadow reflects spotty calcification within the lesional tissue (Fig 24)

With respect to the joint surface, the lesion frequently extends to the articular cartilage and may even protrude perceptibly into the joint. This is particularly true of lesions bordering upon the knee joint, although even in the shoulder joint region, one may observe some destruction of the overlying articular cartilage.



Fig 26 —Roentgenogram of a benign chondroblastoma situated within the head and neck region of the femur of a 20-year-old man. The lesion is fuzzily rarified but well delimited and apparently extends to the articular cartilage of the head. Following thorough curettement and packing with bone chips, the patient made a rapid recovery and regained a full range of painless motion of the hip

Clinical Complaints.—The onset of the condition in the patients was insidious and the complaints had been present for some months before medical attention was sought. As in the case of most tumors of bone, some of the patients related their difficulty to some antecedent injury, but as many more gave no history of

any relevant trauma. All of them referred their complaints to the affected j region (knee, ankle, or shoulder) which was painful on motion, and more or swollen and tender. With involvement of a lower extremity limping was no as was some muscular atrophy of the affected side, and in some instances also, presence of increased fluid in the neighboring joint.



Fig. 27.—A and B. Roentgenograms of a pertinent tumor in a young woman 20 years age which apparently originated in the region of the greater trochanter another unusual lo tion fo it. Positive identification of this tumor from the biopsy sections entailed some d culty but careful search revealed the presence of streaks of calcification within fields of necr tumor tissue. Satisfactory recovery and follow-up observation of the patient after curettem dispelled any lingering doubt that the tumor might represent a malignant neoplasm.

Pathology

Fortunately only an occasional limb is ablated or resected upon the mistak impression that the lesion represents a sarcoma, but when this does happen, o has the opportunity to study an entire intact specimen or at least, a full section of One such resected humeral specimen has been described by Jaffe and me, and Phe ster has observed another. In the former the tumor involved the tubercles, n

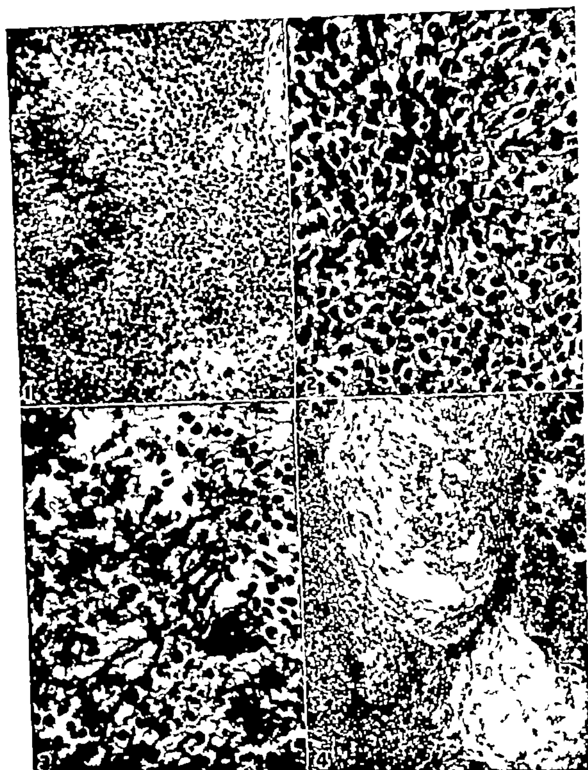


Fig 28.—Representative fields of tumor tissue from the case illustrated in Fig. 26 demonstrating the evolutionary cycle of the lesion. *1* through *4* show focal calcification within the cellular tumor tissue followed by degeneration and necrosis and, eventually resorption of calcific detritus, and connective tissue replacement of necrotic fields leading to the formation of collagenous plaques often resembling osteoid or chondroid matrix.

taphysis, and an adjacent bit of the capital epiphysis of the humerus. The articular cartilage of the head was found preserved almost throughout, but did show small marginal exostoses and a small defect in one area, filled in with connective tissue. In the cut section, the tumor measured 6 cm. in its long axis, and 4 cm. across. The tumor tissue was sharply delimited from the neighboring uninvolved bone, and the delimiting margin was convexly lobulated. Within the limits of the tumor one could clearly discern residual portions of the partially destroyed epiphyseal cartilage plate. Much of the tumor tissue was modified by cystic softening and hemorrhage. The relatively well preserved tumor tissue was gray-brown in color and firm, or more yellowish and gritty from calcification within it (Fig 23 *B*)

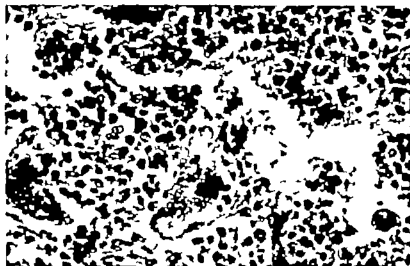


Fig 29 —A field of cellular tumor tissue showing a number of multinuclear cells within and about an area of blood extravasation It is the appearance of such random fields that may cause the lesion to be mistaken at times for giant-cell tumor although its cytologic pattern as a whole should hardly occasion any confusion. (See Fig 28.)

Ordinarily of course, the surgical material available for study and diagnosis consists of small fragments obtained by curettement. In the interpretation of such material it is essential for the pathologist to bear in mind that the cytologic pattern of the lesion frequently varies from specimen to specimen, and even in different fields of the same specimen, reflecting as it does the evolutionary cycle of the lesion. Thus the earliest-phase is represented by cellular tumor fields composed of rather compact, roundish or polyhedral cells of moderate though variable size, with a relatively large nucleus, and sometimes more than one nucleus. Dispersed here and there, there may be a sprinkling of multinuclear giant cells, particularly where hemorrhage has occurred. These multinuclear cells (which account for much of the confusion of this lesion with giant-cell tumor of bone) are not constantly found and, even when present in scattered foci, do not seem to represent an integral part of the cytologic pattern (Fig 29) The readily discernible cue to the diagnosis of benign chondroblastoma is the presence of focal areas of calcification throughout the cellular tumor tissue. Wherever this calcification is particularly heavy, the

tumor cells swell and undergo degeneration and necrosis (after the manner of cartilage cells undergoing calcification preparatory to osseous transformation) Also in the wake of necrosis, and as part of the reparative process, one observes resorption of calcific detritus, organization of hemorrhage, and connective tissue replacement of necrotic fields. This connective tissue may ultimately assume the form of smaller or larger collagenous plaques, sometimes resembling chondroid, but more often osteoid matrix. Finally the latter may in some few fields go on to actual osseous transformation. It is the random intermingling of fields showing various phases of this sequence that often makes the composite cytologic picture seemingly complex (Fig 28)

Treatment and Prognosis

Thorough curettement of the lesion and packing of the cavity thus created with cancellous bone chips appears to be the method of choice. As noted this is likely to have been done in many instances, even before the diagnosis has been established on a histologic basis. Frozen section of a bit of the tumor tissue obtained at time of operation should be sufficiently distinctive in its appearance to warrant an immediate impression in most cases, so that one need not wait upon paraffin sections to clarify the indications for definitive treatment. In those of our cases in which thorough curettement was carried out, the lesion healed without recurrence and good function was restored. The end results in these cases were the same whether or not the curettement had been followed by radiation therapy in moderate dosage. On the other hand in a case in which the lesion was in a femur and in which merely a punch biopsy was taken and the lesion subsequently treated with heavy irradiation, a flexion contracture of the knee resulted, requiring arthrodesis for correction On microscopic examination in this case, islands of viable tumor tissue were still recognizable in the osteoarticular shavings removed in the course of the knee fusion. Altogether the weight of evidence seems to be against the necessity of irradiation and is certainly against very vigorous irradiation either with or without previous curettage.

The prospect of a cure and satisfactory restoration of function in patients properly treated is uniformly good in our experience. In none of our patients was any local recurrence noted after treatment, and this is in keeping with the observations of Codman, all of whose patients (9 in number) were well 3 to 10 years after coming under treatment. What might happen eventually in an untreated tumor is not known. Coley has expressed the opinion that, "It seems not unlikely that some of the late chondromyxosarcomas of the upper humerus may have developed on the basis of untreated epiphyseal chondromatous tumors which had been present since adolescence," but this view is admittedly speculative. Actually no clearly established instance of benign chondroblastoma manifesting spontaneous malignant change has as yet been observed, or at least recorded The only possible exception to this statement with which I am familiar is a case I observed recently through the courtesy of Hatcher In this instance, a chondrosarcoma which proved rapidly fatal in spite of resection developed in the upper end of a humerus of a boy 19

years of age, who 3 years previously had had a benign chondroblastoma in the capital epiphysis of the same bone. This lesion had been thoroughly curetted and then irradiated over a 2 month period postoperatively receiving an estimated total tumor dose of 3 600 r The neoplasm that later developed had no cytologic resemblance to the original lesion and I am inclined to the view that it may well represent a chondrosarcoma induced by x ray irradiation. As strong collateral evidence in support of this view one can cite another comparable case previously reported by Hatcher[8] in which following heavy irradiation of a benign chondroblastoma of the upper tibia, a chondrosarcoma developed in the head of the contiguous fibula.

It may be pertinent here to mention also that Geschickter and Copeland[6] have stressed the importance of distinguishing between benign chondroblastic tumors and "malignant chondroblastomas," though discussing them under a single head and implying that they have a common origin and possibly transitions. It seems to me that their malignant chondroblastomas so-called are actually frank chondrosarcomas readily distinguishable from benign chondroblastoma.

Summary

Benign chondroblastoma of bone is conceived of as a clinically and pathologically distinctive benign neoplasm which has no kinship to genuine giant-cell tumor to which it has nevertheless been linked in the past as the so-called "calcifying" or "epiphyseal chondromatous" variant. *It is my considered opinion that* the neoplasm should be classified more logically among the tumors of bone derived from cartilage cells or cartilage forming connective tissue The tumor originates commonly within the epiphyseal end of a large tubular limb bone, though it frequently extends into the adjacent metaphyseal region. Specifically the femur tibia, and humerus are predilected (in that order) and we have not as yet encountered the tumor elsewhere, although ostensible lesions in hand and foot bones have been reported Also, in our experience, the tumor develops with remarkable consistency in young patients in the second decade and predominantly in males. Cytologically tissue from a lesion may in some fields at least, bear a superficial resemblance to giant-cell tumor of bone, especially if there has been hemorrhagic extravasation. However the readily discernible cue to its recognition is the presence of focal areas of calcification. Where this is particularly heavy the tumor cells undergo degeneration and necrosis, in the wake of which one also observes resorption of calcific detritus organization of hemorrhage, and *fibrous tissue replacement* leading to the formation of dense collagenous plaques resembling chondroid or osteoid matrix.

Although this neoplasm of bone is rather uncommon, its recognition is nevertheless of practical importance, inasmuch as instances of it are not infrequently overdiagnosed as chondrosarcoma or even osteogenic sarcoma, with the attendant recommendation of ablation. Actually the tumor is entirely benign, responding satisfactorily to thorough curettement, and no instances of aggressiveness or spontaneous malignant change have been recorded.

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VII

Chondromyxoid Fibroma of Bone

Chondromyxoid fibroma, a comparatively recent addition to the family of bone tumors, was described and christened by Jaffe and me[11,12] in 1948 on the basis of experience with 8 cases of the lesion. Prior to this, it seems not to have been generally recognized as a distinctive neoplasm, although it appears likely that single instances were reported as enchondroma or myxoma and their malignant counterparts.[4,7,10,18] It is significant that the first two specimens in our own series were originally considered to be chondrosarcomas, and it was not until our entire chondrosarcoma material was surveyed[13] that the pathologic distinctiveness of these particular tumors was fully appreciated. That the tendency to overdiagnosis as sarcoma is still a problem to others is highlighted by a case in point reported by Ottolenghi and Petracchi (1953) as chondromyxosarcoma (in which an entire astragalus was removed when curettement and packing with bone chips would have sufficed for cure). It is true that the tumor presents certain cytologic features which may suggest malignancy to one who is unfamiliar with the lesion, but we have learned empirically that it is benign and does not tend to recur after thorough curettement.

Since the first edition of this book appeared I have had occasion to observe material from many additional instances submitted for consultation, and my experience with this tumor to date now covers more than 30 cases altogether. Increasing awareness of it is evidenced also by the publication of an appreciable number of case reports within the past several years.[2,5,6,9,18]

Chondromyxoid fibroma is a peculiarly differentiated tumor apparently derived from cartilage-forming connective tissue, which exhibits certain chondroid and also myxoid traits that hallmark the lesion cytologically. Basically it is composed of spindle-shaped cells lying loosely in a myxoid intercellular matrix which, as the tumor matures, may undergo substantial collagenization. The tissue of any particular specimen may also come to simulate cartilage tumor tissue in some or many fields, and in its gross appearance it likewise bears a certain resemblance to cartilage. However the tumor is quite distinct from the common enchondroma

which is composed of facets of mature hyaline cartilage, and there is little room for confusion on that score. While chondromyxoid fibroma is not a particularly common neoplasm, its recognition is of some importance in that pathologically, as noted, it may be readily mistaken for sarcoma, especially chondrosarcoma and myxosarcoma and as such treated more radically than is necessary

Clinical Features

Age and Sex Incidence.—Most of the cases observed (approximately two-thirds) have been in comparatively young patients in the second and third decades. The remainder were in older adults, and I have seen but a single instance in a child below the age of 10 years. There appears to be no predilection for either sex.

Localization.—The tumor is encountered most often in the lower extremity particularly in the lower metaphysis of the femur the upper metaphysis of the tibia, the lower end of the fibula or in one or another of the foot bones (especially the metatarsals and calcaneus) In addition, a number have been observed in ribs and in the innominate bone, and an unusual case was reported recently by Benson and Bass that involved the vertebral column (at the level of D 1 to D-3) It seems probable that in time instances of it will be encountered in other sites as well.

Within the upper tibia and lower femur the commonest sites of localization, the tumor was found in the metaphyseal area, as noted, not far from the neighboring joint In these bones the lesion was situated eccentrically eroding and more or less destroying the overlying cortex. In the calcaneus the lesion was likewise eccentrically located in the volar portion of the body at some distance from the apophysis. In small tubular bones, such as the fibula or a metatarsal, the tumor may eventually occupy the entire width of the affected bone area and cause appreciable expansion of it.

Clinical Complaints.—These were of no particular help in diagnosis, except in so far as they directed attention to the presence of a slowly developing lesion within the affected bone. The complaints were usually of some months' duration, if not longer before the patients sought medical attention because of pain particularly on function of the affected part, and in most instances also awareness of a palpable mass. In some of the cases observed there was a history of a previous injury but this is a story that one can elicit from a certain number of patients presenting virtually any bone tumor

Gross Pathologic Features and Their Roentgenographic Reflection

The tissue comprising a lesion of chondromyxoid fibroma is uniformly white, yellowish white, or tan in color solid in texture, and rather firm but rubbery in consistency While its appearance may suggest cartilage tumor tissue on casual inspection, it lacks the facetted pattern and blue white luster of an enchondroma. It should be noted also that, despite the myxoid character of the intercellular matrix observed on microscopic examination, the tissue does not appear at all slimy or mucinous in the gross.

The tumor completely replaces the bone at the site of development, and residua of the original spongy trabeculae are not usually found within it. Where it abuts on the cortex, it tends to erode gradually and destroy the latter, and the contour of the affected bone area becomes bulged. This expanded contour may be outlined, in part or throughout, by a thin shell of periosteal new bone. Where a delimiting cortical shell is absent, the tumor is still confined by the periosteum and the overlying parosteal connective tissue, and it exhibits no tendency to be invasive. Internally when the tumor does not extend across the entire width of the bone, it is bordered, as a rule by a clearly outlined bed of sclerotized and often distinctly notched osseous tissue.

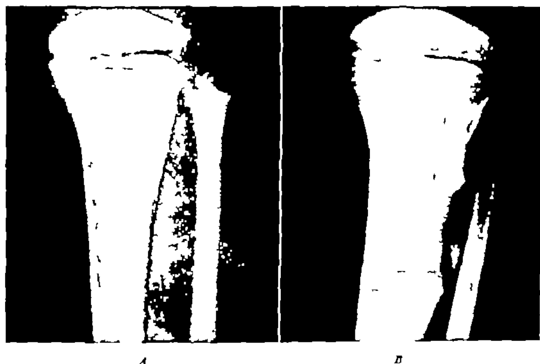


Fig 30—*A* Roentgenogram of a chondromyxoid fibroma in a young boy developing in the upper metaphysis of a tibia, a frequent site of localization *B* Recurrence of the tumor illustrated in *A* after apparently inadequate curettement Although this was disturbing clinically the recurrent growth was sharply delimited internally by a zone of sclerotized bone, which was somewhat grooved or scalloped, and peripherally by a shell of cortical new bone. The surgeon elected to do a wide block excision, but thorough curettement and packing with bone chips would have sufficed for cure

These gross features of the lesion are reflected in its roentgenographic appearance. It should be noted that the tumor may attain appreciable size, although occasionally it is discovered while still quite small. Among the tumors I have observed, there were some which measured as much as 7 or 8 cm. in length and 4 or 5 cm. across. Within a large limb bone, as indicated, the tumor tends to be eccentrically located in the metaphyseal area and does not ordinarily encroach upon the bone end. The contour of the tumor may appear roundish but is more

often ovoid, and its long axis coincides with the long axis of the affected bone. The area occupied by the lesion appears relatively radiolucent. The external border of such a tumor as noted tends to be outlined by a more or less expanded delicate shell of periosteal new bone, although the latter may be defective in places. Its internal border is outlined by a well-defined, oftentimes scalloped, sclerotized line. The grooved and notched character of this perifocal bone may also cause the projection of the lesion to appear pseudotrabeculated. Altogether these features



A. B

Fig 31.—A Representative roentgenogram of a chondromyxoid fibroma situated in the lower shaft and metaphysis of a femur, another frequent site of localization. Tumors such as this are sometimes treated more aggressively than is required. B Another chondromyxoid fibroma situated in the lower end of the fibula of a man, aged 30 years. The lesion was known to have been present for 8 years.

tend to give the lesion a rather distinctive appearance which enables one to recognize it even before surgery (Figs 30 and 31). When the tumor is still comparatively small, however, or when it presents in a rib or in a foot bone as an expanded lesion extending across the entire width of the affected bone, it is more difficult to identify (Figs 32 and 33). In such instances, though one may still suspect its presence, one would also have to consider such alternatives as a solitary focus of fibrous dysplasia, enchondroma, and possibly aneurysmal bone cyst.



Fig. 32.—*A* Roentgenogram of a pertinent expanded, rarefied, and pseudotrabeculated lesion replacing the distal phalanx of a toe in an adult. The biopsy sections were originally interpreted as indicating the presence of a malignant myxoid tumor so that amputation of the distal end of the phalanx was performed. *B* Another chondromyxoid fibroma in the metatarsal bone of a great toe, which has expanded and replaced the entire bone except for a small portion of the head. The patient a 56-year-old man had complained of pain for about 3 years. Treatment consisted of curettage and insertion of an inlay bone graft and led to a satisfactory result. There was no indication of local recurrence 3½ years later



Fig 33—Roentgenogram of an unusual chondromyxoid fibroma (reported by Benson and Bass) that involved the vertebral column at the level of D-1 to 3 encroached upon the spinal canal, and caused symptoms of spinal cord compression. The symptoms were effectively relieved by surgery and supplementary x ray therapy



Fig 34 —Roentgenogram of another chondromyxoid fibroma situated within a pubic bone. Its cytologic picture is illustrated in Fig 35 A This roentgen picture of the lesion as it appears in a flat bone lacks the distinctiveness of those illustrated in Fig 30.

Microscopic Appearance

The cytologic picture presented by any particular lesion of chondromyxoid fibroma varies somewhat with its age or what one may regard as its degree of maturation. In general, increasing maturity appears to be reflected in progressive collagenization of the intercellular matrix of the lesion. In some instances the matrix acquires a chondroid appearance as well. Be that as it may the basic cytologic pattern is that of fields of tumor cells of spindle or multipolar shape rather loosely dispersed within a myxoid intercellular matrix. This lesional tissue tends to be demarcated into pseudolobules by narrow, vascularized, curving bands of more compacted tumor cells. Within these myxoid fields, the tumor cells on the whole, have indistinct cytoplasmic borders, although many of them show branching fibrillar processes. The cell nuclei, as indicated, are for the most part spindle-shaped, ovoid, or multipolar and stand out prominently The supporting connective tissue is somewhat vacuolated and has a bluish hue when stained with hematoxylin. When sections are stained for the demonstration of mucin, the intercellular matrix does not give the mucin response, and it seems probable that the myxoid character of the matrix is attributable to its aqueous content rather than mucin (Fig 35)

At the periphery of the pseudolobules particularly one is likely to find more compacted tumor cells with prominent nuclei. Some or even many of these cells may present large plump nuclei, strikingly hyperchromatic nuclei, or atypical large double or multiple nuclei, creating an unduly ominous impression, if one is

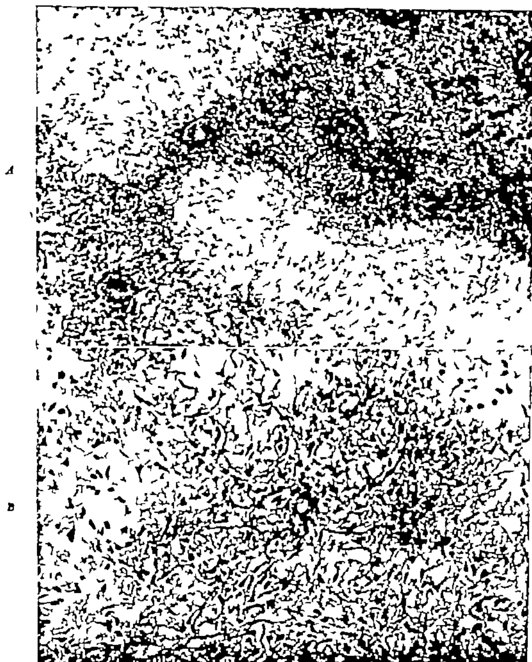


Fig. 33.—*A* and *B*. Photomicrographs showing the general cytologic pattern of the tumors illustrated roentgenographically in Figs. 31 and 33 respectively. The spindle-shaped tumor cells are loosely dispersed in a myxoid intercellular matrix. There are also occasional fields (in the upper illustration) which have acquired a chondroid appearance. (×100)

unfamiliar with the lesion. In this vicinity also and especially around the blood vessels within tracts of supporting connective tissue, one may observe evidence of blood extravasation and the presence of occasional multinuclear giant cells and hemosiderin laden macrophages, along with a number of small mononuclear cells and polymorphonuclear leukocytes. Here also there may be macrophages containing sudanophilic droplets and occasional small nests of foam cells. It should be noted that the presence of multinuclear cells within the connective tissue framework may sometimes cause the lesion to be mistaken for giant-cell tumor even though the cytologic pattern of the lesion as a whole is quite at variance with that of genuine giant-cell tumor To cite a case in point, the neoplasm illustrated by Willis[17] in his monograph on tumors as a "chondromatous osteoclastoma" is undoubtedly an instance of chondromyxoid fibroma (Fig 36)

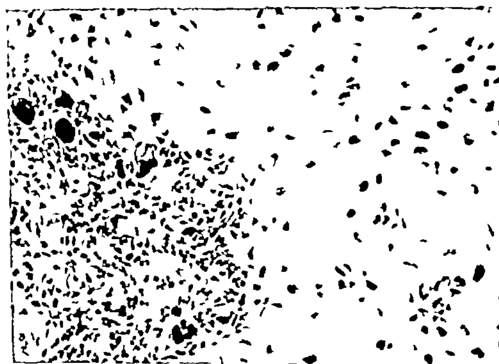


Fig. 36.—Photomicrograph of another pertinent lesion showing the presence of several multinuclear cells within a tract of supporting connective tissue, though not within the lesional tissue proper It is the appearance of such fields that may cause the lesion to be interpreted as a peculiar giant-cell tumor (×135.)

In the more mature tumors, while a tendency toward lobular arrangement may still be maintained, one observes evidence of appreciable collagenization of the intercellular matrix, either focally or throughout. In such areas, a loose network of crisscrossing collagen fibers can be demonstrated by appropriate stains. In some lesions, these collagen fibers are interwoven into a compact mat, and smaller or larger hyaline patches may develop In an occasional lesion, a few small foci of calcification and ossification may be noted, but this is likely to be an incon

spicuous feature. In the older tumors also, the matrix tends to take on a chondroid appearance in places, and in such fields many of the tumor cells come to lie in lacunae, so that the area as a whole acquires a certain resemblance to cartilage. This chondroid appearance, considered in conjunction with the presence of tumor cells with prominent hyperchromatic nuclei and cells with two or more nuclei, accounts for the fact that chondromyxoid fibroma is often mistaken for chondrosarcoma by pathologists who are not familiar with the lesion (Fig 37) By the same token when the intercellular matrix is predominantly myxoid rather than chondroid, one can readily understand how a diagnosis of myxosarcoma might be entertained. It should be emphasized, however that in spite of any seemingly ominous cytologic features which may be present, the biologic behavior of the neoplasm is that of a benign tumor Metaphorically speaking chondromyxoid fibroma of bone is a neoplasm whose bark is worse than its bite.

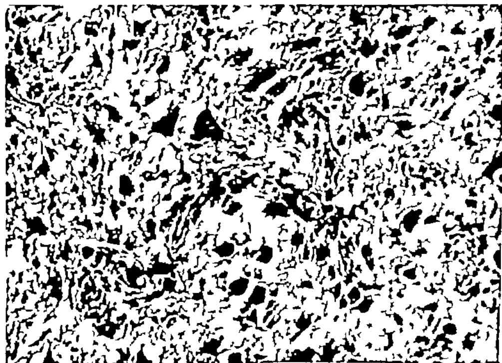


Fig 37 —Photomicrograph of a selected field of a chondromyxoid fibroma showing the presence of numerous ominous-looking multinuclear cells. The latter should not be regarded as an indication of malignancy this particular tumor was actually quite indolent in its growth. (×275)

It remains to consider in passing the question of the possible relationship of chondromyxoid fibroma to so-called myxoma of bone. This is rather difficult to answer particularly since the existence of a pure myxoma of bone analogous to myxoma (or myxosarcoma) of skeletal soft parts has not been firmly established. It is almost impossible, for instance, to determine from the papers of Bloodgood, dealing ostensibly with "myxoma of bone," precisely what the tumors described

actually represent, although it is my impression that the more aggressive ones may well have been chondrosarcomas exhibiting secondary myxoid change. Viewing the question from an academic standpoint, if one defines myxoma as a mesenchymal connective tissue neoplasm of soft, slimy appearance, containing abundant mucin within its ground substance, then chondromyxoid fibroma fails to meet these criteria. Further, if one compares the tissue of a chondromyxoid fibroma with that of an umbilical cord, one finds but little resemblance between them. Nevertheless, it would appear that the tumor under discussion is sometimes misinterpreted as a myxoma of bone, and it is interesting to note that at least one of the tumors reported by Bloodgood under that head seems to be a case in point. This applies also to the instance reported by Bauer and Harrell (1954) in the lower metaphysis of the femur of a 12 year-old boy.

Treatment and Prognosis

As indicated, the tumor appears to be entirely benign in its clinical behavior and none of the instances of it that I have observed have shown any tendency to recur after thorough curettement, even without supplementary irradiation. The necessity for reasonably complete curettement, however, to avoid possible local recurrence has been stressed by Dahlin, and this appears to be sound advice. When the tumor has attained appreciable size, the cavity created by curettage is sufficiently large to warrant filling the defect with bone chips or using an inlay graft for support. Since all of our patients were surgically treated, I have had no experience by which to judge the effectiveness of radiation therapy against the tumor.

Of the original series of 8 cases reported, postoperative follow up records were available in 6, for periods ranging from 1½ to 7 years, and in none of these was there any clinical or roentgen evidence of local recurrence. One would seem wholly justified, therefore, in forecasting a clinical cure in any pertinent case following thorough curettement. It is, of course, possible that the malignant counterpart of chondromyxoid fibroma does exist, but I have never encountered it nor am I aware of any such instances in the literature.

Summary

The tumor designated as chondromyxoid fibroma of bone seems not to have been generally recognized in the past as a distinctive neoplasm, although it appears likely that single instances of it have been reported as enchondroma or myxoma and their malignant counterparts. An occasional instance may also be *mistaken for an unusual giant-cell tumor*. Our interpretation of the lesion is that of a peculiarly differentiated connective tissue tumor exhibiting in the course of its evolution certain chondroid and also myxoid traits which hallmark the lesion cytologically. It is composed basically of cells lying loosely in a myxoid intercellular matrix which, as the tumor matures, may undergo substantial collagenization. The tissue of any particular tumor may also come to simulate cartilage tumor tissue in some or many fields, and in its gross appearance it likewise bears a certain resemblance to cartilage. There are, however, distinct differences between

the appearance of this tumor and that of the common garden variety of enchondroma. The presence of smaller or larger numbers of tumor cells exhibiting nuclear atypism may cause the lesion to appear more ominous than we know it to be, explaining why it is frequently overdiagnosed as a malignant tumor and, particularly as chondrosarcoma.

My total experience to date with this tumor comprises some 32 cases, and increasing awareness of it is evidenced also by the publication of an appreciable number of case reports within the past several years. The tumor is encountered most often in one or another bone of a lower limb although instances have been observed in ribs, the innominate bone, and the vertebral column as well. Most of the patients were adolescents or young adults, though some were older The lesion as a rule, evolves slowly and is often of some months or even several years standing before surgical treatment is sought. Within the femur and tibia, the commonest sites of localization, the lesion was found consistently in the metaphyseal area adjacent to the knee joint and was eccentrically located The roentgenographic picture has a certain distinctiveness, at least when the lesion is in a large limb bone and has attained appreciable size, although its differentiation at times from aneurysmal bone cyst, enchondroma, or a focus of fibrous dysplasia may be difficult without tissue examination. The tumor is apparently entirely benign and does not tend to recur after thorough curettage even without supplementary irradiation. While the tumor is not a particularly common one its recognition is of some importance in that, pathologically it may be readily mistaken for a sarcoma, especially chondrosarcoma or myxosarcoma and, as such, treated more radically than is necessary

Other Benign Chondroid Tumors

The view has been expressed recently by Dahlin[8] that chondromyxoid fibroma and benign chondroblastoma are closely related pathologically in that certain tumors held to be chondromyxoid fibromas may show fields reminiscent of benign chondroblastoma and vice versa. It is true that one occasionally observes tumors composed of partially differentiated cartilage forming connective tissue, some of which appear to be developing in the direction of chondromyxoid fibroma and others in the direction of benign chondroblastoma. Still others may show cytologic features reminiscent of both these neoplasms, and an occasional one may be composed of more primitive spindle connective tissue cells, forming only a few inconspicuous patches of chondroid matrix to reveal its basic character Altogether I have observed material from 15 such tumors to date (occurring in adults as well as in youngsters) most of which were situated within the lower limb especially in foot bones. A few were encountered within phalanges of fingers. Although the cellularity and poorly differentiated character of some of them are calculated to arouse a strong suspicion of malignancy their clinical behavior has not been at all aggressive. Study of this group of tumors strongly supports the concept that chondromyxoid fibroma and benign chondroblastoma are closely related members of the same family of tumors of cartilage-forming connective-tissue derivation—first

cousins, if not siblings. It seems a mistake however and a step backward not to maintain the separate identity of fully evolved tumors of the nature of chondromyxoid fibroma and benign chondroblastoma respectively

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VIII

Osteoid-Osteoma

The concept of osteoid-osteoma, once controversial, has now won general acceptance and any questions that remain are of greater academic than practical import. Osteoid-osteoma was first described as a distinctive benign osteoblastic tumor by Jaffe[7] in 1935 in a paper reporting 5 relevant instances developing within spongy bone. Subsequently Jaffe and I[8] observed that the same lesion frequently *developed also in relation to the cortices of the shafts of long bones and that when* it did so, it provoked remarkable sclerosis of the surrounding cortex out of proportion to the small size of the nidus. Such cases had previously been commonly misclassified (and still are though less often) as instances of cortical bone abscess or of sclerosing nonsuppurative osteomyelitis. Incidentally it was never maintained that there was not a sclerosing form of osteomyelitis (Garré's osteomyelitis) but only that some or many cases so-called proved on closer scrutiny to be instances of osteoid-osteoma. The report of this further experience with the lesion was published in 1940 and dealt with 33 cases in all. The relative frequency of the lesion was further demonstrated by the fact that Jaffe[9] in 1945 was able to report on 62 proved cases, and the tally at present undoubtedly exceeds 100. Additional observations of value on sizeable groups of cases have now been reported from many centers.

It is interesting to note in passing that the concept met with a good deal of resistance at first from a number of orthopedists and radiologists reluctant to give up the idea of a low-grade infection as a basis for the condition,[3] but it gradually won over as stout adherents[2, 8, 12, 14, 16, 19] all but a few die-hard skeptics.[1] At the present time even those who have some reservation as to whether the lesion represents a genuine neoplasm readily accept the fact that it is highly distinctive and clearly recognizable roentgenographically and pathologically It is freely admitted that there are still a number of questions which we are not as yet able to answer satisfactorily but these do not relate to the identity of the lesion. Why is the lesion so small, as a rule? Why is it invariably painful? What would happen to the lesion ultimately if it were left undisturbed? What is the effect of x ray irradiation upon it?

An osteoid-osteoma may be defined as a small oval or roundish tumorlike nidus which is composed of osteoid and trabeculae of newly formed bone deposited within a substratum of highly vascularized osteogenic connective tissue The lesion even when it is fully evolved usually does not exceed a centimeter in its greatest dimension. It may develop either within the spongiosa, often at or near an articular surface, or in relation to the cortex of the affected bone. In the latter situation, the lesion may be located within the cortex or abut against its inner surface When it develops within a spongy bone area, it provokes merely a thin rim of reactive sclerosis around it, but when it develops in relation to the cortex of a long bone, for some reason or other one commonly observes a perifocal zone of dense sclerotized cortical bone extending for a considerable distance beyond the osteoid-osteoma per se. The lesion may be encountered in young children, but is seen more often in adolescents and young adults. It is distinctly uncommon beyond the age of 30 years. The site of the lesion was found to be a tibia or a femur in about half of the cases. Involvement of other bones in the lower extremity, particularly the foot bones, is also fairly common. Less common, though by no means unusual is localization in a bone of an upper limb or in the vertebral column (usually the arch rather than a body) I have seen but a single instance in a rib (the 12th) of a young woman who had complained of pain in that site for 3 to 4 years. A noteworthy instance has been described as occurring in a mandible, but to my knowledge the lesion has not as yet been observed in the calvarium.

It may be mentioned here that Lapidus and Salem[11] have reported a case in which it is claimed from the roentgen findings that two separate osteoid-osteoma lesions were present in a femur However the identity of only one of these lesions was established by pathologic examination Another presumptive case reported from Upsala, Sweden, as bilateral symmetrical osteoid-osteoma appeared to me on review of the available sections to be an instance of bilateral osteoperiostitis, provoking localized cortical thickening

Diagnosis

Clinical Complaints.—The duration of symptoms at the time the patient seeks treatment usually varies from about 6 months to 2 years. I am familiar with a case in which the complaints were of fully seven years duration, and it is interesting to note that the osteoid-osteoma removed from this patient, with prompt and complete relief as usual, showed no indication whatsoever of spontaneous involution. The major complaint referable to the tumor is pain, mild and occasional at first but increasing in persistence and severity so that ultimately it often keeps the patient awake at night. It is noteworthy also that this bone pain is often relieved by aspirin. Local swelling may become apparent in some instances and, in most a sharply localized point of exquisite tenderness over the painful area can be demonstrated. Only rarely does one note slight local heat and redness, and in none of our cases was there a history of a febrile episode in connection with the lesion.

Roentgen Diagnosis.—The diagnosis of osteoid-osteoma is not difficult usually if one is familiar with its clinical peculiarities and if it has advanced sufficiently in its evolution to be clearly demonstrable roentgenographically. In occasional instances, the devolpment of distressing pain may antedate the clear demonstration of the offending lesion in roentgenograms of the affected part (e.g., an astragalus

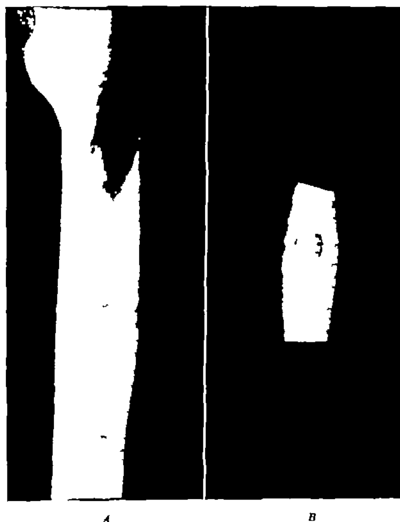


Fig. 38.—*A*, Roentgenogram of an osteoid-osteoma nidus developing within the cortex of the shaft of a femur. The lesion, though comparatively small, has provoked considerable perifocal cortical thickening. *B*, Roentgenogram of the surgically excised cortical block incorporating the lesion. The latter is relatively radiopaque and the thin lucent halo around it marks its junction with the surrounding thickened cortex.

or calcaneus) by some months or even a year or more. In such instances, the patients may be regarded for a time as malingerers or psychoneurotics. There may also be some lag in the recognition of a nidus which develops beneath the articular cartilage of a long bone, or of one which is situated within a facet or a lamina of a

vertebral body In a pertinent case presenting a characteristic roentgen picture the osteoid-osteoma nidus appears as a small oval or roundish focus which is usually relatively radiolucent, but may occasionally be radiopaque The shadow of this nidus is often, though by no means regularly surrounded by a more or less dense shadow reflecting the reactive sclerosis of the neighboring bone. This sclerotized



Fig. 39—*A* Roentgenogram showing an osteoid-osteoma within the thickened cortex of the lower femur (of a young man who had complained of persistent, distressing localized pain in that area) Although the original x ray film (received from abroad) was of rather poor quality the offending osteoid-osteoma nidus can be clearly visualized. *B* Photograph (natural size) of a surgically extirpated block of thickened cortical bone from a comparable case, showing an encoffined small ovoid lesion of osteoid-osteoma

zone around the nidus may be only a narrow ring, or it may spread for several centimeters about the lesion, even when the latter is situated in the spongiosa. If the lesion develops within or just beneath a shaft cortex, the perifocal densified area may extend for several inches above and below the lesion. Further the thickening

of the cortex may be found to extend for a considerable distance around the circumference of the affected shaft area tending to obscure the small lesion which provokes it. In such cases, overexposing the film and coning down on the affected area in various planes may enable one to discern the central nidus more readily although in occasional instances in which the latter is relatively radiopaque even this procedure is not successful.

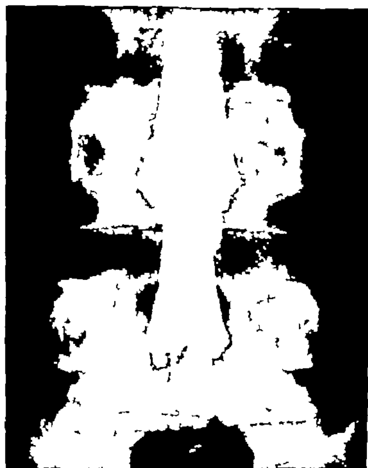


Fig 40.—Roentgenogram of the lumbar spine of a 22 year-old man presenting a sciatic syndrome clinically for over 2 years and distressing low back pain for 1 year. Surgical exploration revealed the presence of a circumscribed, globular osteod-osteoma focus, 7 mm. in diameter (clearly visualized in the roentgenogram) situated within the inferior facet of the fifth lumbar vertebra. Its removal resulted in complete relief of pain.

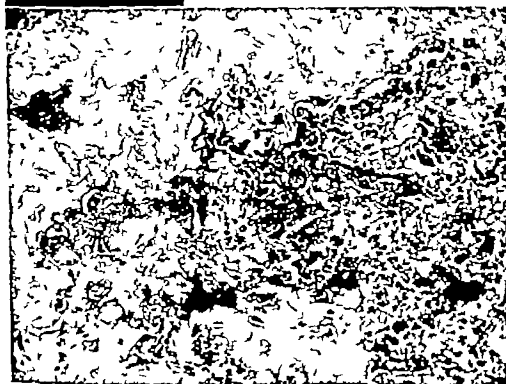
The major problem in differential diagnosis is to distinguish between osteoid osteoma and the occasional instance of relatively small intracortical bone abscess which may simulate it. On occasion also, it may be difficult on the basis of the roentgen picture alone to distinguish osteoid-osteoma from chronic sclerosing osteomyelitis. In such cases, one must take into consideration the clinical findings as well and definitive answer may have to wait on pathologic examination of the surgical specimen.

Pathology

When an osteoid-osteoma in a spongy bone area is removed intact in its setting or at least removed without fragmentation or crumbling it stands out strikingly in the gross as a circumscribed reddish bony focus When a thickened cortical bone block containing a nidus in its interior is excised serial slices made preferably with a band saw will reveal the encoffined nidus in one or two of the blocks (Fig 42 A) The lesion is very likely to be situated at the junction of the



A



B

Fig. 41 —A Roentgenogram of a resected head of a radius which includes the major portion of an osteoid-osteoma. This was not visualized in the clinical films because the bones of the elbow were heavily overlaid by periosteal new bone resulting from an injury The surgical procedure afforded prompt relief of pain B Photomicrograph of a field of the osteoid-osteoma illustrated in A which is still composed largely of osteoid undergoing calcification and conversion to atypical bone. (×70)

new and old cortex or somewhat deeper toward the medullary cavity When the nidus has been broken up into small fragments (by a chisel or curette) the latter may be mistaken for bits of granulation tissue, although they can be clearly identified as portions of an osteoid-osteoma by an experienced observer on microscopic examination. (*Fig* 45)

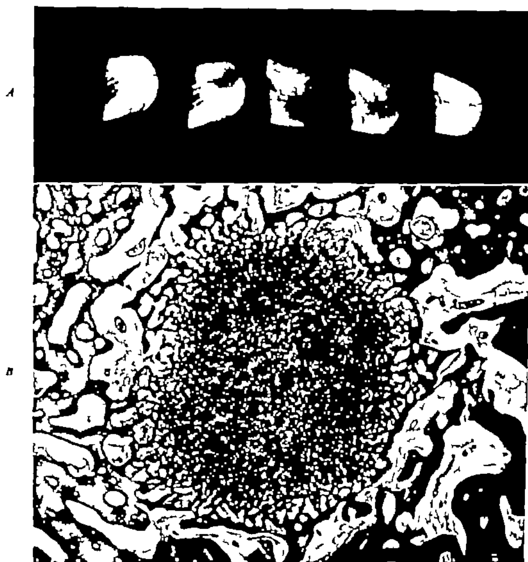


Fig 42 — 4 Roentgenogram of serial slices of an osteoid-osteoma encoffined within the thickened cortical bone of the shaft of a femur The specimen was excised en bloc and sectioned with a band saw *B* Photomicrograph of the osteoid-osteoma nidus illustrated in *A* It is composed of irregularly calcified osteoid and new bone.

In microscopic sections the lesion stands out sharply as a circumscribed focus of osteoid and more or less calcified atypical bone developing within a background of richly vascular osteoblastic connective tissue. Some lesions are composed in large part of compact osteoid. In other lesions, apparently the older ones, these

sheets of osteoid have already been split up and remodeled into trabeculae, which become calcified and converted to atypical bone. This is essentially the picture of the fully evolved lesion. On the other hand it has been rather difficult from the material available to trace satisfactorily the genesis of the lesion from the very beginning and the earlier stages of its evolution require further clarification. This much we do know however. We have observed a number of pertinent specimens



Fig. 43.—*A* Roentgenogram of a small osteoid-osteoma developing beneath the cortex of the distal phalanx of a fifth finger of a boy 14 years of age who had complained of pain for about a year. The circumscribed dense nidus is surrounded by a radiolucent halo. *B* Photomicrograph showing the topography of the osteoid-osteoma illustrated in *A* (×20)

from cortical locations particularly which indicate that initially at the site in the cortex where the lesion is developing a peculiar condensation and an intense reconstruction and vascularization of the original cortical bone sets in. The latter is soon substantially resorbed though perhaps not completely and is replaced by highly atypical osseous tissue deposited apparently by the osteogenic connective tissue which is carried in along with the blood vessels that are invading the area. While this focus of bone is undergoing creeping replacement and reconstruction,

the overlying periosteum may be depositing a thick layer of new bone, the architecture of which is rather normal aside from its condensation. Within this reactive new cortical bone, one may observe small focal collections of lymphocytes in the immediate vicinity of the nidus, but this feature apparently reflects nothing more than an expression of chronic irritation.

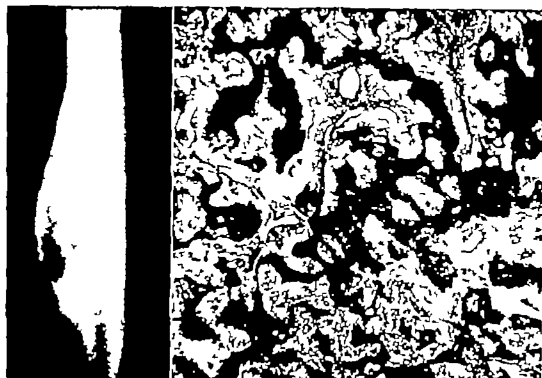


Fig 44.—A Roentgenogram of an osteoid-osteoma of unusual size, which has provoked marked cortical thickening of the shaft of the humerus. The patient was a young man 20 years of age who had complained of dull aching pain as well as swelling, of the affected side. In the clinical roentgenograms, the lesion proper measured as much as 5 cm. in its long axis. Surgical treatment consisted of thorough curettement through a large cortical window which effected complete lasting relief of symptoms. B, Photomicrograph of a selected field of the lesion illustrated in A, showing heavily calcified, large irregular patches of osteoid. Other fields showed a more conventional, readily discernible picture of osteoid-osteoma, remarkable only in that its connective tissue was inordinately vascular (×40) (From Lichtenstein, L. Benign Osteoblastoma Cancer 9 1044 1956)

As to the interpretation of the lesion of osteoid-osteoma, we still feel confident on the basis of the additional experience we have had since 1940 in affirming that this peculiar lesion of bone is unique and that it does not represent a response to infection. The evidence against the idea that osteoid-osteoma may have an infectious inflammatory basis will not be repeated here, and for a detailed analysis of that question the reader is referred to our article published in 1940. In that paper we also explain why we do not believe that the osteoid-osteoma lesion represents a peculiar healing or reparative form of some other familiar lesion, or

that it originates from an embryonic rest Altogether, we have been led both by the process of elimination and by consideration of the anatomic characteristics of the lesion itself to the conclusion that it is best interpreted as a neoplasm, and specifically as a peculiar benign tumor of bone of osteoblastic connective tissue derivation. Added support for this concept comes from the observation of a number of remarkably large osteoid-osteomas, one of which (in the shaft of a humerus of a young adult) measured as much as 5 cm. in its long axis. (Fig 44) Another comparable instance was encountered in the lamina of a lumbar vertebra of a child. Still another cogent argument for the tumorous nature of osteoid-osteoma can be based upon the strong cytologic resemblance of some lesions of osteoid-osteoma, in part or substantially throughout, to certain instances of benign osteoblastoma the neoplastic nature of which can hardly be disputed (Chapter 9)

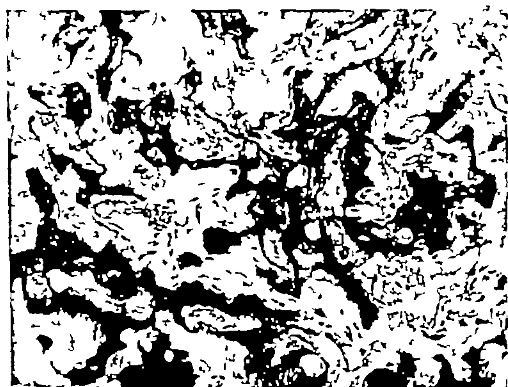


Fig 43 —Photomicrograph of a field of another osteoid-osteoma which was fragmented and removed piecemeal by curette rather than excised en bloc. Patches of osteoid are undergoing irregular heavy calcification and conversion to atypical bone and show also invasion by tracts of rather vascular osteoblastic connective tissue. The identification of a lesion such as this hinges on the ability of the pathologist to recognize its distinctiveness.

Treatment and Prognosis

As noted surgical removal of the lesion will effect almost immediate and lasting relief. In none of our cases in which the lesion was completely removed surgically was there any recurrence, and invariably the pain caused by the lesion disappeared with dramatic promptness. The nidus and some of the surrounding

bone may be removed by curettement, but this should be thorough, since otherwise there is danger of recurrence of the complaints. If the osteoid-osteoma nidus is missed on surgical intervention (e.g., one situated deep within the neck or intertrochanteric region of a femur may be difficult to localize) pain will recur after a short interval and increasing perifocal sclerosis will manifest itself. For this reason it is strongly advised that x-ray control be utilized to aid in effective localization and to make certain before the operation is concluded that the osteoid-osteoma nidus has actually been removed. In the case of lesions embedded within thickened shaft cortices we have been advocating block resection in order to obtain the nidus, whenever possible, intact in its setting for more complete and satisfactory pathologic examination. However, it is not essential for clinical cure to remove all of the thickened perifocal bone or even a substantial part of it. When such a case is explored, it may be helpful in the matter of localization to bear in mind that the osteoid-osteoma focus is likely to be situated directly beneath the point of greatest convexity of the thickened cortical surface.

The ultimate fate of an untreated lesion is not known, although we have seen a number of cases in which the clinical complaints were of several years' duration (in one instance as long as seven years) and in which the nidus eventually removed at surgery showed no indication of change in the direction of involution. Also, we have little relevant information in regard to the possible effectiveness of irradiation in the treatment of osteoid-osteoma. In a case cited by Jaffe, x-ray irradiation (2,000 r., total dose) of a pertinent lesion in the humerus of a 15-year-old boy afforded relief for 3 years, but recurrence of pain eventually necessitated surgical excision. It seems to me that this modality should be reserved for lesions in surgically inaccessible sites (e.g., in the upper cervical spine).

Summary

The lesion designated as osteoid-osteoma is a highly distinctive one and seems best interpreted as a peculiar benign tumor of osteoblastic derivation. The condition is not uncommon, and our experience with it now exceeds 100 cases. It is encountered mainly in older children, adolescents, and young adults below the age of 30 years. Although it may affect almost any bone, it predilects the bones of the lower extremity, especially the femur and tibia. It is a small roundish or ovoid lesion which usually does not exceed a centimeter in its greatest dimension, although I have observed some that were substantially larger. It may develop in the spongiosa or in the cortex of the affected bone, and it stands out from the surrounding osseous tissue as a sharply delimited nidus. This is usually composed of osteoid and more or less calcified atypical new bone which can be seen to have developed out of a rather vascular osteogenic connective tissue. When an osteoid-osteoma develops in the spongiosa, a narrow or even fairly wide zone of the surrounding spongy osseous tissue usually becomes densified and sclerotic. When it develops within or just beneath the cortex, the latter tends to become markedly thickened, mainly through periosteal new bone formation, and if the lesion develops in the cortex of a long bone, as it often does, the reactive cortical thickening may be very striking and out of proportion to the size of the offending nidus.

The diagnosis of osteoid-osteoma is not difficult in most instances if one is familiar with its clinical peculiarities and if the lesion has advanced sufficiently in its evolution to be clearly demonstrable roentgenographically In interpreting the roentgenographic picture in a case of osteoid-osteoma, one must remember that this picture has two aspects—that of the lesion proper and that of the reaction which it has provoked around it. The osteoid-osteoma proper is usually indicated by a relatively radiolucent area, although, if it has become substantially calcified and ossified, it may appear as a relatively radiopaque nidus. In the cortex of a long bone, one may have difficulty in clearly distinguishing the osteoid-osteoma shadow if the reactive cortical thickening is considerable or if the lesion has become ossified, since its shadow may then be dominated by that of the thickened cortex. Because the roentgenographic picture has these two aspects, a case of osteoid osteoma in a spongy bone area may be mislabeled as chronic osteomyelitis with bone abscess or with an annular sequestrum. Similarly a case of osteoid-osteoma in the shaft of a long bone may be mislabeled as sclerosing non-suppurative osteomyelitis of Garré or intracortical bone abscess.

The presenting symptoms clinically are localized tenderness and pain, usually of at least several months duration, which may be persistent and severe enough to awaken the patient at night. The clinical findings do not point to an infectious inflammatory basis for the disorder Complete surgical excision of the osteoid osteoma proper with or without some of the surrounding bone, results in clinical cure with prompt and often dramatic relief of distressing pain. Following incomplete removal of an osteoid-osteoma (usually in a site where accurate localization is difficult) one may expect only temporary relief followed by return of pain requiring a second exploration. In no case in which the lesion was completely removed surgically has there been a recurrence.

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IX

Benign Osteoblastoma

In this section I have attempted to delineate more clearly the pathologic nature and appropriate treatment of certain benign tumors of bone of osteoblastic derivation, other than osteoid-osteoma and osteoma so-called. Their recognition is of practical importance in that they may be mistaken for giant-cell tumor or osteogenic sarcoma and, as such treated more aggressively than is required. The writer has had occasion within the past several years to observe material from 11 pertinent instances encountered in long bones, the vertebral column, and other sites that will serve as the basis for discussion.[7]

These benign osteoblastic tumors include the ones previously called "osteogenic fibroma" by me, as well as those referred to provisionally as "other osteoid tissue-forming tumors" in my classification of primary tumors of bone.[8] I have come to feel that there is no fundamental difference between these two subgroups and that for all practical purposes they comprise a single category of benign osteoid and bone-forming tumors which may be appropriately designated as benign osteoblastoma. With reference to relevant cases previously published under other titles, it seems altogether probable that the unusual neoplasm described by Jaffe and Mayer[4] as an "osteoblastic osteoid tissue forming tumor of a metacarpal bone" falls logically into this category Furthermore, most of the tumors recently reported by Dahlin and Johnson under the heading of "Giant Osteoid Osteoma" are undoubtedly cases in point (benign osteoblastomas) although a few may be plausibly interpreted as genuine osteoid-osteomas. I am reluctant to adopt this proposed name, however if only for the reason that the concept of classical osteoid-osteoma has become too firmly established and useful to be vitiated by the inclusion of other tumors differing in a number of essential respects, clinically and radiologically as well as pathologically If the designation of giant osteoid-osteoma is to have any usefulness within the present framework of reference, it might apply rather in a literal sense to the genuine osteoid-osteomas of unusual size that one encounters occasionally As previously noted, I have had the opportunity to observe two such remarkably large osteoid-osteomas, one in the lamina of a lumbar vertebra of a child and the other in the shaft of the humerus of a young adult (Fig 44)

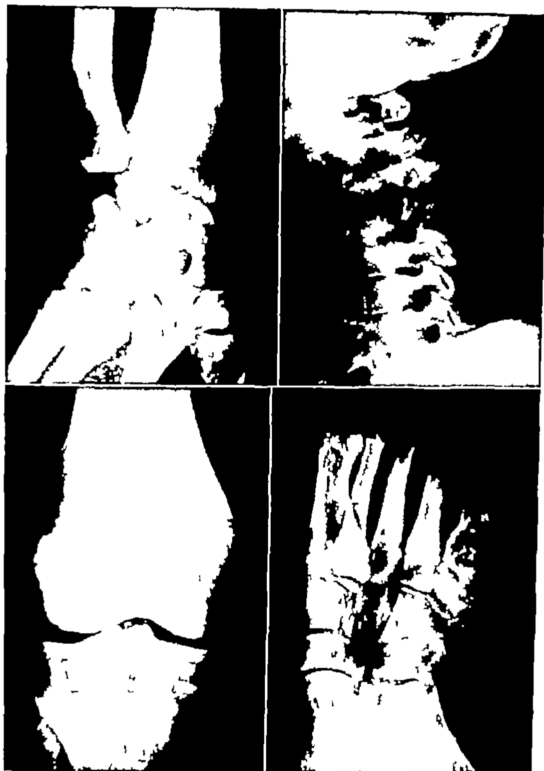


Fig 46—*A* Roentgenogram of a benign osteoblastoma situated in the lower end of a radius in an adult. It has expanded and attenuated the overlying cortex but is well delimited by a delicate shell of periosteal new bone, while its internal border is sharply outlined by a sclerotized line. The clinical symptoms were of at least 2 years duration. *B* Roentgenogram of another

(Legend continued on opposite page.)

In the matter of nomenclature it may be remarked further that the choice of the name "osteogenic fibroma of bone" has seemed to misfire, as it were, although it has been employed by a few investigators, notably Golding and Sissons. It has apparently tended to puzzle pathologists generally in that the term "fibroma" however qualified conventionally carries the connotation of a fibroblastic tumor whereas the neoplasms under discussion are essentially osteoblastic. For this and other reasons, it is suggested that "osteoblastoma" is perhaps a more appropriate name qualified as "benign" to make certain that it is not confused with osteogenic sarcoma. The tumors in point exhibit appreciable variation in cytologic detail (Figs. 49 and 50) which will be considered further on, but their common basic pattern is readily recognizable if one becomes familiar with it. The important thing is to avoid being confused by their content of multinuclear cells, mainly osteoclasts about trabeculae of osteoid and new bone, and to recognize clearly that their richly vascular osteoblastic connective tissue stroma is not that of a sarcoma.

Clinical Features

Age and Sex Incidence.—While the number of cases presented at this time is statistically small, it seems significant that as many as 7 of the 11 patients were children or teen-age (6 9 12, 14 16, 18 and 18 years of age respectively) There did not appear to be any predilection for either sex.

Localization.—The majority of the tumors in this series were encountered either in long bones or in the vertebral column, although there were several situated elsewhere. Specifically their distribution was as follows 4 in limb bones (lower metaphysis of the femur tibial shaft [2] and lower end of the radius) 4 in the vertebral column (spinous process of C-3 spinous process of C-4 neural arch of D 2, and the neural arch of L-1) 2 in the calvarium (temporal bone) 1 in a foot bone (metatarsal) It seems altogether probable that, with increased experience, instances of this tumor will be encountered in other sites as well.

Clinical Complaints.—The major complaints were pain often of insidious onset and/or palpable slightly tender swelling that increased perceptibly under observation. On the whole the clinical findings in themselves were not sufficiently distinctive to be of much help in differential diagnosis. The pain was not of the

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osteoblastoma (in a child 6 years of age) that has expanded the spinous process and encroached upon the body of C-4 The expanded portion of the tumor is well outlined peripherally *C* Roentgenogram of a benign osteoblastoma situated eccentrically in the lower metaphysis of the femur of a 14 year-old girl who had complained of pain for several *months. Like the tumor* illustrated in *A* it is delimited peripherally by a thin shell of periosteal new bone and internally by a sclerotized border The sections were interpreted by one consultant pathologist as showing a giant-cell tumor and by another as a sarcoma with the recommendation of amputation. The lesion was treated by curettement and packing with bone chips, and at the last follow-up 8 months later the patient had made a complete recovery *D* Roentgenogram of a tumor that has markedly expanded the base and proximal shaft of a fifth metatarsal bone and shows fine radiopaque stippling reflecting new bone formation. (A D from Lichtenstein L., Benign Osteoblastoma Cancer 9: 1011 1956)

type commonly encountered with osteoid-osteoma in that it did not tend to awaken the patient at night or to be relieved especially by aspirin. The duration of symptoms prior to surgery ranged from a few months to as long as 2 years.

It is noteworthy that the lesions developing in the neural arch of a vertebra (rather than its spinous process) gradually induced compression of the spinal cord, manifested by weakness and eventually paraplegia that required surgical intervention for relief. This complication was also noted in two comparable instances reported by Golding and Sissons. Incidentally, their first tumor was regarded provisionally as an osteogenic sarcoma and, as such, was heavily irradiated (total dosage of 5 000 r), while the second also received as much as 3 600 r postoperatively on the mistaken premise that it represented a giant-cell tumor (osteoclastoma).

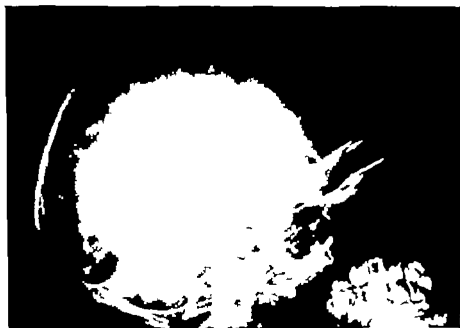


Fig. 47.—Roentgenogram of a circumscribed tumor in the right temporal bone of a 9-year-old girl which had slowly increased in size over a period of 2 years. It had provoked slight reactive sclerosis around most of its periphery. The tumor measured 3.5 cm. in its greatest dimension and 2.5 cm. in thickness and was found at surgical exploration to have expanded both tables of the calvarium. The patient was entirely well at the last follow-up 15 months after local excision. (From Lichtenstein, L.: Benign Osteoblastoma, Cancer 9: 1044, 1956.)

Roentgen-Ray Picture.—For convenient orientation a number of representative roentgenograms are illustrated in Figs. 46, 47 and 48. While they tend to convey the impression of a benign neoplasm, the picture as a whole is not nearly so distinctive as that of some other benign tumors of bone. This much seems clear, however. Irrespective of size and location, the tumor tends to be well circumscribed. When it has attenuated and expanded the overlying cortex, as it often does, it is still delimited by a delicate shell of periosteal new bone. Incidentally, in no instance

observed was there pronounced cortical new bone formation surrounding the lesion as occurs with osteoid-osteoma arising within or beneath the cortex of a large limb bone[3] (Fig 44) Along its internal border the tumor tends to be delimited by a sclerotized margin testifying to its relatively slow rate of growth. The lesion itself may be essentially radiolucent or on the other hand, exhibit soft or somewhat



Fig 48.—*A* Roentgenogram of another benign osteoblastoma in the shaft of the tibia of a 12 year-old girl which is somewhat unusual in that it presents a large central bony focus. *B* The latter was excised (with the thought that it might represent an osteoid-osteoma), but the lesion was otherwise not disturbed. *C* Follow up roentgenograms taken 14 months later show restoration of a good, thick intact cortex and no increase in the size of the residual tumor by actual measurement. Photomicrographs of this tumor are illustrated in Fig. 50 *B* and *C* (From Lichtenstein L. Benign Osteoblastoma Cancer 9 1044 1956.)

harder radiopaque mottling (depending upon the extent of focal calcification of osteoid and its conversion to bone) The instance in the shaft of the tibia illustrated in Fig 48 is exceptional apparently in that it presents a large ovoid nidus of dense bone in its interior

Pathologic Features

Gross Appearance.—Inasmuch as the available specimens consisted of fragments obtained by curettement or piecemeal resection, the gross character of the lesional tissue must be determined largely from the surgeons' operative findings. The impression gained from the available data is that of granular or more friable, essentially gritty tissue, gray brown or reddish brown in color and richly vascular on the whole.

Microscopic Findings.—The basic picture observed in the instances studied is essentially that of a well vascularized osteoblastic connective tissue stroma in which osteoid and new bone are deposited commonly though not invariably in rather orderly trabecular pattern (Fig 49 *A* *B* and *C*) As noted, there are variations in detail from case to case. In particular the extent of calcification of the osteoid deposits varies appreciably it may be relatively slight and inconspicuous (Fig 49 *D*) or on the other hand one may observe heavy focal calcification of osteoid and conversion to trabeculae of atypical bone (Fig 50 *A* and *B*) These latter fields, especially may be reminiscent of comparable fields of an osteoid osteoma (Fig 50 *A*)

The stromal cells may be roundish, ovoid or more spindly in one tumor or another and their compactness or the relative cellularity also may vary Their cytoplasmic borders appear fairly distinct. In proximity to mineralized deposits, *they tend to swell up and to be more closely approximated and altogether come to* resemble active osteoblasts. Here also they are prone to surround the intercellular matrix and eventually to become enveloped by it. Whatever the size, shape, or number of the osteoblastic stromal cells may be it is significant that they show neither appreciable dissimilarity nor any significant cellular or nuclear atypism and few if any mitoses.

The multinuclear macrophages (giant cells) that may be present are especially prominent within and about vascular spaces and also in close proximity to trabeculae of osteoid and/or new bone, the remodeling of which (by osteoclasts) apparently starts relatively early It is the abundance of these skeletal macrophages oftentimes that may cause some instances to be mistaken for giant-cell tumor though without sound justification. At times the tumor tissue between mineralized deposits is permeated by numerous dilated and engorged thin walled vascular channels, about which there may be considerable blood extravasation. This great vascularity obviously favors active osteogenesis as well as the appearance of giant-cell macrophages.

Differentiation From Other Lesions

It has already been intimated that the cytologic pattern of a number of the tumors studied (Fig 50, *A*) though by no means all, was sufficiently reminiscent of *osteoid-osteoma* as to suggest a close pathologic relationship Incidentally this cytologic resemblance would seem to lend support to the view that osteoid-osteoma represents a genuine benign neoplasm of bone. It should be emphasized however

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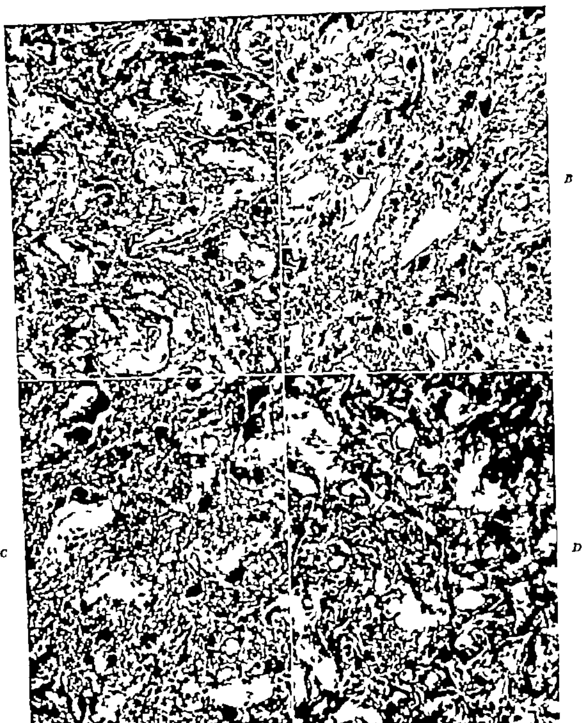


Fig. 49.—*A*, *B* and *C*, Representative photomicrographs of a number of benign osteoblastomas showing in common rather orderly deposition of trabeculae of osteoid and new bone within a richly vascularized background of osteoblastic connective tissue. Multinuclear macrophages, mainly osteoclasts, are prominent here and may suggest giant-cell tumor to an inexperienced observer (×110, ×110, and ×160 respectively). *D*, Photomicrograph of another tumor showing extensive deposition of only partially reconstructed osteoid as its salient feature. Tumors such as this may be mistaken for osteogenic sarcoma even though their stroma is hardly that of a malignant neoplasm (×200). (*A–D* from Lichtenstein, L.: Benign Osteoblastoma, Cancer 9: 1044, 1956.)

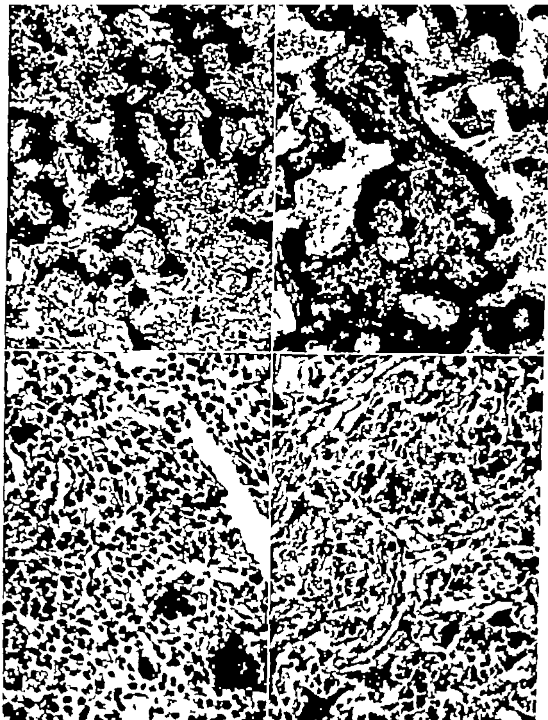


Fig 50.—*A* Photomicrograph of still another tumor showing a pattern reminiscent of osteoid osteoma. This particular lesion was a thumb-shaped gritty tumor measuring 3.5 cm. in length, that had compressed the spinal cord extradurally at the level of D 2 (×110.) *B* Photomicrograph of a selected field of the tumor in the tibia illustrated in Fig 48. The trabeculae of atypically calcified new bone here have a more irregular pattern. (×150) *C* A relatively cellular field of the tumor illustrated in *B* showing compact round or ovoid stromal cells that have as yet laid down but little osteoid matrix. These cells, however are relatively small and essentially uniform and, as such, are not calculated to create the impression of a sarcoma (×340) *D* Photomicrograph of a representative field of another pertinent tumor (in the calvarium) showing relatively cellular osteoblastic stroma The osteoblasts between and about trabeculae of calcifying osteoid are distinctly plump but quite uniform and the soundness of the impression of a benign tumor was borne out by the clinical result (×210.) (*A–D* from Lichtenstein, L. Benign Osteoblastoma, Cancer 9: 1044 1956.)





Fig 51 – 4 Roentgenogram showing an osteoma so called protruding into a frontal sinus. *B* Photomicrograph of a representative field of the osteoma of the calvarium illustrated in *A* showing prominent formation of plaques and trabeculae of new bone within an osteoblastic connective tissue matrix. (×100.)

that benign osteoblastomas differ from classical osteoid-osteoma in that they are substantially larger are not of sharply defined spherical or ovoid contour do not present a roentgen-ray picture remotely suggestive of osteoid-osteoma, and do not induce the characteristic history of persistent localized bone pain associated with that lesion. Conceived in a very broad sense osteoid-osteoma and so-called osteoma (of the orbit and paranasal bones particularly) may be regarded as special types of benign osteoblastoma. As indicated however there are distinct advantages to retaining their separate established identities, although they may well represent related members of the same family of benign tumors of osteoblastic derivation.

Fibrous Dysplasia—Although there has been a tendency in the past to label some solitary lesions of fibrous dysplasia showing appreciable new bone formation, especially in jaw bones, as fibrous osteoma" or "ossifying fibroma (benign osteoblastoma in the present terminology) their accurate differentiation microscopically should not occasion much difficulty Lesions of fibrous dysplasia are on the whole more fibrous and less vascular and their trabeculae of new bone, being formed *by metaplasia of the connective tissue, are not rimmed by osteoblasts, as are lesions* of benign osteoblastoma (Figs. 205 to 207)

Giant-Cell Tumor.—As for differentiation from giant-cell tumor cytologically (apart from distinct clinical differences) this may conceivably be a problem if one is dealing with a needle aspiration biopsy but not otherwise. Suffice it to reiterate that the irregularly dispersed multinuclear cells observed represent osteoclasts or macrophages in proximity to blood vessels or within fields of blood extravasation, rather than syncytial tumor cells Moreover prominent osteoid and bone formations are not an integral feature of genuine giant-cell tumor

Osteogenic Sarcoma.—The distinction between benign osteoblastoma and osteogenic sarcoma may prove troublesome at times if one attempts to base opinion upon a small biopsy specimen without benefit of the roentgenograms and good clinical orientation—a practice that should be heartily discouraged in general. As noted, an occasional benign osteoblastoma may present a relatively compact stroma, but the cells appear quite uniform and the intercellular matrix is deposited in a rather orderly trabecular pattern, as a rule. If one observes irregular heavy columns or long crisscrossing streamers of osteoid and/or new bone, one must then be circumspect about the strong possibility of osteogenic sarcoma. Notwithstanding it seems that some pathologists still tend to be stampeded by the sight of active new-bone formation, regardless of circumstances. Thus, the tumor illustrated in Fig 46 *C* was interpreted as a sarcoma by one consultant who examined the sections, while the tumor illustrated in Fig 46 *D* was thought to be malignant by about 60 per cent of the pathologists who saw it at a statewide slide conference.[8]

Treatment and Prognosis

Surgical treatment should be conservative, in keeping with the benign character of the tumor When the latter is of relatively small or moderate size, thorough curettement and packing with bone chips appears to be the procedure of choice. Also when the tumor is situated in the calvarium conservative curettement or resection should suffice for clinical cure, and there appears to be no necessity for

sacrificing any wide margin of surrounding intact bone or resorting to supplementary irradiation. When the tumor is located in a spinous process of a vertebra local excision is calculated to give a satisfactory clinical result. In dealing with a lesion in the neural arch of a vertebra that has induced weakness or paraplegia, one must at least excise the tissue responsible for extradural compression of the spinal cord or its nerve roots, although it may be difficult in this situation to effect complete removal

The limited growth potential of the neoplasm is convincingly demonstrated by the sequence of events in the instance in the shaft of the tibia illustrated in Fig 48 In this case, because of the extent of the lesion and uncertainty as to its nature, the surgeon elected to do only a limited biopsy and to remove the radiopaque focus in the interior of the lesion (thought possibly to represent an osteoid-osteoma nidus) without attempting thorough curettement. Despite only partial extirpation roentgenograms taken 14 months later showed reconstruction of the cortical defect without measurable increase in the size of the lesion.

In nine of the eleven cases presented, follow-up data were obtained covering intervals ranging from 7 months to 3 years after surgical treatment. In none of these was local recurrence noted roentgenographically and the clinical results were correspondingly satisfactory It is significant that this favorable trend was noted also in the relevant cases reported by Dahlin and Johnson, in many of which the follow-up observations covered a much longer period, ranging up to 19 years. In one instance in the present series (in which a localized tumor of the neural arch of L-2 had caused cord compression) follow up information could not be elicited.

The question of recurrence and eventual malignant change after a long latent interval was raised in only one exceptional instance in which the tumor involved the laminae and pedicles of L-1 and L-2 and impinged upon the spinal roots. In this case, there had been local recurrence of the bone-forming neoplasm and return of symptoms fully 9 years after laminectomy and piecemeal incomplete removal of a modrate-sized tumor followed by roentgen-ray irradiation. Partial extirpation of the recurrent tumor accomplished decompression and relief of symptoms as readily as it had initially Examination of the sections, however showed distinct increase in cellularity and enlargement of the nuclei of the osteoblastic stromal cells as compared with the original slides. Although the appearance of the recurrent tumor could hardly be characterized as that of a frank osteogenic sarcoma, it seemed prudent to venture a guarded prognosis, and this patient will bear further close follow-up.

Summary

This section attempts to delineate the pathologic nature and appropriate treatment of certain benign osteoblastic tumors, other than classical osteoid-osteoma and osteoma so-called on the basis of experience with 11 pertinent instances encountered in long bones, the vertebral column, and other sites. The name "benign osteoblastoma" is employed to designate appropriately this caetgory of osteoid and bone forming tumors, including those previously called "osteogenic fibromas," among

others. Their recognition is of particular importance in that they may be mistaken for giant-cell tumor osteogenic sarcoma and, as such, treated more aggressively than is required.

Addendum.—Since this chapter was written I have had occasion to observe material from some 4 additional pertinent instances of benign osteoblastoma situated in the shaft of a humerus the proximal tibia, a temporal bone, and a rib respectively These have not caused me to alter significantly any of the views expressed above.

References

1 Dahlin, D C., and Johnson, E. W Jr Giant Osteoid Osteoma J Bone & Joint Surg. 36-A: 559-572, 1954
2 Golding, J S. R., and Sissons, H. A Osteogenic Fibroma of Bone; a Report of Two Cases, J Bone & Joint Surg 36-B: 428-435 1954
3 Jaffe, H L., and Lichtenstein, L. Osteoid-Osteoma Further Experience With This Benign Tumor of Bone With Special Reference to Cases Showing the Lesion in Relation to Shaft Cortices and Commonly Misclassified as Instances of Sclerosing Non Suppurative Osteomyelitis or Cortical Bone Abscess, J Bone & Joint Surg 22: 645-682, 1940 (Figs. 10 22, & 27)
4. Jaffe, H L., and Mayer L. An Osteoblastic Osteoid Tissue Forming Tumor of a Metacarpal Bone, Arch Surg 24: 550-561 1932.
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7 Lichtenstein, L. Benign Osteoblastoma, Cancer 9: 1044-1052 1956.
8 Stewart F W. Personal communication December 9 1954.

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4. Jaffe, H. L., and Mayer, L.: An Osteoblastic Osteoid Tissue-Forming Tumor of a Metacarpal Bone, Arch. Surg. 24: 550-564, 1932.
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of involvement. In any event, the lesion is usually found in the shaft, toward the upper or lower end of the bone and extending, as a rule, within an inch or two of the adjacent epiphyseal plate.

Clinical Complaints.—There is nothing characteristic about the clinical history nor is the latter particularly helpful in diagnosis, except in so far as it directs attention to the necessity for roentgen examination. In most instances the complaints are of brief duration, although this does not mean that the lesion was not of longer standing developing slowly and insidiously before it was discovered. Many patients complain of pain and swelling of an ankle, knee, or wrist and

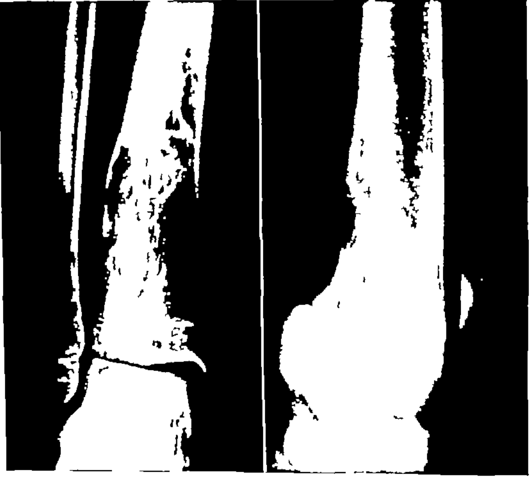


Fig. 12.—A Roentgenogram of a non-osteogenic fibroma in the lower shaft of a tibia of a 15-year-old boy which was discovered following an injury to the ankle. The lesion is eccentrically situated, loculated and sharply delimited internally by sclerotized bone. The overlying cortex is in part thinned and slightly bulging. This picture is so characteristic of the lesion as to lea e little doubt as to its identity even before tissue examination. The tumor in this instance was thoroughly curetted and packed with bone chips. B Another clinically silent lesion of non-osteogenic fibroma in the lower end of a femur discovered on roentgen

By way of orientation, it should be pointed out that the lesion under consideration has in the past been classed by some among the giant-cell tumor variants, so-called, and specifically as the healing or spindle-cell or xanthic variant,[3,4,5] although, as will be indicated presently it has virtually nothing in common clinically with genuine giant-cell tumor Nor is there anything about the cytologic appearance of the lesion to suggest giant-cell tumor other than the presence, as noted, of occasional multinuclear cells within its whorled spindle connective tissue. Further some instances of the lesion under discussion have been interpreted as representing xanthoma or xanthogranuloma[1,2] of bone, so-called, or as a localized expression of lipoid granulomatosis, mainly because the basic connective tissue cells in places have taken up lipid and become converted to nests of foam cells. This aspect of the lesion, prominent though it may be in some instances, appears to represent a secondary change rather than an essential feature, and one encounters many pertinent instances in which the presence of lipid cannot be demonstrated even in serial sections stained with Sudan. On occasion also, the lesion may be overdiagnosed by pathologists unfamiliar with it as low-grade fibrosarcoma or osteolytic osteogenic sarcoma with the attendant hazard of unnecessary ablation. It should be noted, further that the lesion has been confused also with monostotic fibrous dysplasia, even though its connective tissue exhibits no tendency to osseous metaplasia. Finally there are those (Hatcher in particular and some others[7,8] following his lead) who have held that the lesion may conceivably result from a local disturbance of bone growth and have referred to it somewhat vaguely as a fibrous metaphyseal defect. In this connection, one must distinguish clearly between non-osteogenic fibroma and the comparatively small, circular or ovoid, rarefied growth defects observed not infrequently in the metaphyses of large limb bones of children, especially in the distal femoral metaphysis.[10] These so-called small growth defects present an entirely different roentgen picture and tend to disappear spontaneously under observation. The interpretation of bona fide non-osteogenic fibroma as a growth defect hardly seems plausible to me, since I clearly recall a proved instance of non-osteogenic fibroma which in successive roentgenograms taken prior to surgery was observed to double and quadruple in size over a period of not more than 2 years. It is true however that the growth tends eventually to become stationary and I have not as yet observed, and have no knowledge of any instance in which, a non-osteogenic fibroma of bone manifested malignant change to fibrosarcoma.

Clinical Features

Age and Sex Incidence and Localization.—The tumor is encountered notably in older children and adolescents, although an occasional lesion, presumably of long standing may be discovered incidentally on roentgen examination of an adult. There does not appear to be any predilection for either sex. As for localization, the tumor is encountered regularly in long limb bones, as noted ... have not as yet observed it elsewhere. As indic... it is the lower ... particularly that are predilected, and specific ... femur and ... ugh occasionally a bone of an upper lim... ulna or hu... be the site

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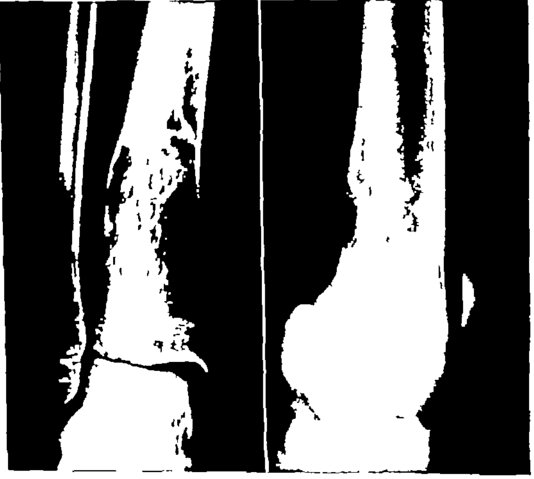


Fig 2-1 Roentgenogram of a non-osteogenic fibroma in the lower shaft of a tibia of a 15-year-old boy which was discovered following an injury to the ankle. The lesion is eccentrically situated, loculated, and sharply delimited internally by sclerotized bone. *The overlying cortex is in* part thinned and slightly bulging. This picture is so characteristic of the lesion as to lea e little doubt as to its identity even before tissue examination. The tumor in this instance was thoroughly curetted and packed with bone chips. *B* Another clinically silent lesion of non-osteogenic fibroma in the lower end *of a femur discovered* on roentgen survey in a patient who also presented an osteogenic sarcoma in the opposite femur

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Fig 52—*A* Roentgenogram of a non-osteogenic fibroma in the lower shaft of a tibia of a 15 year-old boy which was discovered following an injury to the ankle. The lesion is eccentrically situated loculated, and sharply delimited internally by sclerosized bone. The overlying cortex is in part thinned and slightly bulging. This picture is so characteristic of the lesion as to leave little doubt as to its identity even before tissue examination. The tumor in this instance was thoroughly curetted and packed with bone chips. *B* Another clinically silent lesion of non-osteogenic fibroma in the lower end of a femur discovered on roentgen survey in a patient who also presented an osteogenic sarcoma in the opposite femur

attribute their difficulty to some trauma such as a sprain kick or fall to the region in which the bone lesion was discovered Others while giving no history of trauma, likewise had pain and swelling of a joint as their chief complaint. Occasionally pathologic fracture through the attenuated cortex overlying the lesion may be the first manifestation of its presence. In many instances a clinically silent lesion may be discovered as an incidental finding on roentgen examination of the part for some other skeletal difficulty Thus, I have observed several cases of osteogenic sarcoma of the lower femur in which x ray examination of the knee region revealed also the presence of an unsuspected non-osteogenic fibroma of the upper tibia.



Fig 53 —*A* Roentgenogram of a non-osteogenic fibroma in one of its more common sites. Note its subcortical position and its sharp delimitation by a zone of sclerotized bone. *B* Another pertinent lesion in the lower shaft of a fibula. In a small limb bone like a fibula (or an ulna) the lesion may occupy the entire width of the affected bone, and its roentgen picture then becomes more equivocal and not readily distinguishable from that of a small bone cyst or a focus of fibrous dysplasia.

Roentgenographic Findings

Most instances of non-osteogenic fibroma present so distinctive a roentgenographic appearance as to be readily recognizable, if one is familiar with the picture. The usual location of the lesion in the upper or lower third of a long bone at some distance from the adjacent epiphyseal cartilage plate has already been emphasized. In a large limb bone, like the tibia or femur the lesion is found characteristically



Fig 54

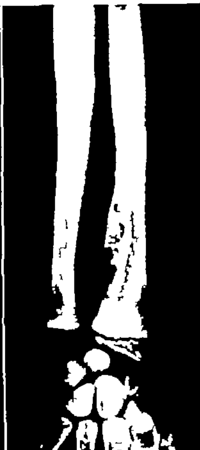


Fig 55

Fig 54.—Roentgenogram of a relatively large, non-osteogenic fibroma situated within the upper shaft of a humerus, an unusual location for it The patient was a boy aged 6 years, who had sustained a pathologic fracture in a fall some 6 weeks previously The tumor tissue on curettement was found to be solid and yellowish in color

Fig 55 —Another pertinent lesion situated beneath the cortex of the lower metaphysis of a radius in a child.

to have an eccentric position abutting on the inner aspect of the cortex, and to be sharply outlined internally by a sclerotized line. The lesion itself casts a rarefied shadow which may appear loculated, owing to the presence of thin, dividing, bony partitions. The cortex delimiting the lesion peripherally is often thinned and sometimes slightly expanded, but its continuity is preserved, unless

there has been a pathologic fracture. As to size, the lesion may be rather small or as much as 5 cm. in greatest dimension, but, in any event, its long axis coincides with that of the bone in which it arises.

When the lesion develops in a slender limb bone, such as the fibula or ulna, it tends to occupy the entire width of the bone and to bring about some expansion and attenuation of the overlying cortex. Its appearance is otherwise essentially similar to that presented by lesions in large limb bones, but one cannot then be certain without tissue examination that one is not dealing with a bone cyst or a solitary focus of fibrous dysplasia. Even when the lesion occupies a central position, its sharply defined and sclerotized outline should preclude any serious thought of giant-cell tumor of bone, as should also its metaphyseal or shaft location and its common occurrence in patients below the age of 20 years.

Since the first edition of this book was published (1952) I have had occasion to observe several remarkable instances in which two or more lesions of non-osteogenic fibroma were found in the lower femur and upper tibia of one limb or the other or both. Such cases are exceptional however and by way of differentiation, one must be alert to the possibility of hyperparathyroidism.

Pathologic Features

Whether the lesion is eccentric in position and abutting on the cortex or whether it extends across the entire width of the shaft, it usually consists of several discrete but contiguous foci of gray yellow or yellow-brown, firm, fibrous connective tissue. *Each focus may be outlined in part by a thin shell of sclerotic bone, and* some of the individual foci may also be separated from each other by bits of sclerotic spongiosa. As for the overlying cortex, this may show endosteal erosion and thinning in some places, and thickening in others. The periosteum of the affected portion of the shaft is not particularly thickened, except at the site of a pathologic fracture.

On microscopic examination as noted, the general pattern of the lesion is that of whorled bundles of connective tissue cells. However the cellularity of the stroma varies from one lesion to another or even from one focus to another within the same lesion. There is also some variation in regard to the vascularity of the lesion, the prominence of multinuclear giant cells within it, and its content of lipid, if any in the form of collections of foam cells. In a distinctly brown lesion or focus, the connective tissue cells are spindle-shaped and closely compacted, being interspersed with but little collagenous intercellular material. Many of the stromal cells are likely to contain granules of hemosiderin in their cytoplasm, and it is mainly this that accounts for the brownish color of the lesion as a whole, although some scattered capillary hemorrhages may also contribute to it. *Irregularly dispersed among* the stromal cells are small often elongated multinuclear giant cells. These cells, sparse on the whole may be more numerous and clustered together in some fields, especially about areas of recent capillary hemorrhage. The giant cells seem to be formed through fusion of the spindle-shaped stromal cells, and, like the latter many of them contain granules of hemosiderin in their cytoplasm.

In a distinctly yellowish lesion or focus, nests of lipoid-containing foam cells are seen, admixed with and encircled by the stromal tissue The latter then consists of rather collagenous spindle-shaped connective tissue cells in winding thick strands or whorled bundles, honeycombed by the foam cells (Fig 57 *B*) It can be shown that these lipid-containing cells arise through conversion of the spindle cells into lipophages, and that the lipids contained within the latter are, to a large extent, of the nature of cholesterol esters. On the whole, the more yellow the lesion or focus, the more lipophages does it contain and the more collagenous does the intervening stromal tissue appear and furthermore the less does it show of hemosiderin pigment in the stromal cells, or of multinuclear giant cells among them. Why the disappearance of the hemosiderin pigment and giant cells should parallel the appearance of foam cells in the lesion we do not know but the fact that it does so is clear from the findings in areas representing intermediary stages of yellow or brown pigmentation.



Fig. 56.—Photomicrograph of a pertinent lesion (in a fibula). Its cytologic pattern is that of whorled, compact, small spindle-shaped connective tissue cells, interspersed among which are scattered, spindly multinuclear cells. The cortical bone has been attenuated and somewhat expanded. (×35.)

Thus in an individual lesion, one may see fields in which the stromal connective tissue cells are rich in hemosiderin and interspersed with giant cells, and other fields in which pigment bearing cells and giant cells are sparse or absent and foam cells are numerous. However in about *half of our cases*, the entire lesion failed to show any lipid at all although the latter was sought for in frozen sections of material stained for fat, and foam cells were looked for in paraffin sections pre-

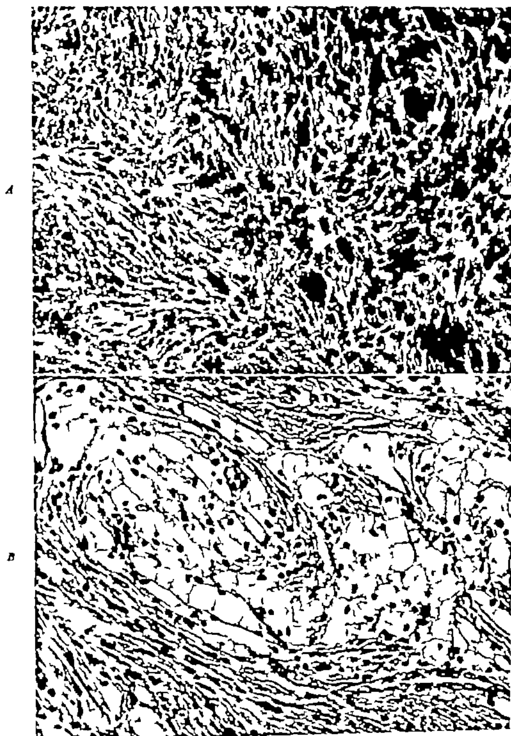


Fig 57.—*A* Photomicrograph of a field of a non-osteogenic fibroma showing occasional small compressed multinuclear cells within the connective tissue stroma. It is the presence of such multinuclear cells that may cause the lesion to be mistaken at times for giant-cell tumor (×250.) *B* Another field of a non-osteogenic fibroma in which the connective tissue cells have taken up lipid and been converted to foam cells. This feature is not a constant one and is observed only in certain lesions, some of which have been labeled in the past as "xanthoma" or "xanthogranuloma." (×250.)

pared from many areas of each lesion It seems clearly unjustifiable therefore to place undue emphasis upon the inconstant lipid component by designating the lesion a xanthoma or xanthofibroma of bone.

Furthermore, none of the lesions examined showed evidence of osteogenesis as a feature of their cytology and the lack of bone formation within these lesions is a consistent and striking finding It is true that individual foci may be walled off or delimited at their periphery by a narrow zone of bone. Also where it abuts upon the cortex of the shaft, the lesion may provoke thickening of the cortex in places, just as, in other places, it may erode it. However in either case, such bone formation represents a response of the neighboring tissue to the lesion and is not a feature of the lesion itself

Treatment

The x ray appearance of the lesion is so consistently distinctive that, in most cases, I now believe that biopsy or surgical removal is elective rather than mandatory However non-osteogenic fibroma of bone is readily amenable to treatment. The patients discussed in this paper were all treated surgically the procedure in most cases being thorough curettement of the lesion In several cases in which the lesion was in the fibula, subperiosteal resection of the affected portion of the bone was done. This seemed the easiest way of completely eradicating the focus of the disease in these particular cases though, even in slender long bones, resection may not always be necessary There were no local recurrences in any of the patients surgically treated. None of them received postoperative radiation therapy

Whether the lesion would be amenable to radiation therapy alone (that is, without surgical intervention) I cannot state from personal experience. Of course, without the histologic examination of tissue made possible by surgical intervention one could not be absolutely certain that the lesion being treated actually represented a non-osteogenic fibroma of bone. Furthermore, I am sufficiently impressed by recent observations on the prevalence of post irradiation sarcomas of bone to refrain from advocating x-ray therapy for benign tumors of bone which can be readily cured by conservative surgery

Summary

Non-osteogenic fibroma of bone is conceived of as a distinctive benign tumor formed from mature marrow connective tissue which exhibits no tendency to osseous metaplasia. Most of the patients presenting the condition are older children or adolescents of either sex. There are no characteristic clinical manifestations and, in fact, the lesion may be entirely asymptomatic, being discovered oftentimes on incidental roentgen examination or following a pathologic fracture. The usual site of the lesion is the shaft of a long tubular bone, most commonly of a lower limb not far from the adjacent epiphyseal cartilage plate. The lesion tends to be of limited size and may not traverse the entire diameter of the affected bone, especially if the latter is a femur or tibia. Roentgenographically such a lesion presents as a sharply delimited eccentric, somewhat loculated area of rarefaction,

hugging and perhaps bulging out the cortex on one side. On the other hand, a lesion in a slender limb bone such as a fibula or ulna, may appear as a multilocular area of rarefaction traversing the bone and even bulging it out on both sides.

On gross pathologic examination the lesion is found usually to consist of several discrete but contiguous yellow-brown fibrous foci. The basic microscopic pattern is that of whorled bundles of spindle-shaped connective tissue cells loosely interspersed with small multinuclear giant cells, though in some lesions, areas containing foam cells may also be present.

In regard to treatment, thorough curettement or block resection of the affected area is all that is needed to effect a cure. *In dealing with a lesion which is not* giving rise to clinical difficulties and whose nature seems reasonably clear from its roentgen appearance, surgical removal is elective rather than mandatory. Nonosteogenic fibroma is an entirely benign lesion, and, if its connective tissue possesses any potentiality of aggressive growth or malignant change I have never observed it.

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XI

Giant-Cell Tumor of Bone (Osteoclastoma)

The subject of giant-cell tumor of bone is one that has been in a state of confusion for a long time not so much because genuine instances of it are difficult to recognize (quite the contrary) as because the diagnosis of giant-cell tumor is frequently applied indiscriminately to other bone lesions, mainly because they present a scattering of multinuclear cells. It is true that noteworthy progress has been made since the rather chaotic situation prevailing some 20 years ago when no clear distinction was drawn between the brown tumors, so-called of advanced hyperparathyroidism and the bona fide giant-cell tumors of surgical practice when, collaterally the neoplastic nature of giant-cell tumor of bone was open to question when a wide variety of unrelated and generally less serious skeletal lesions were arbitrarily associated with giant-cell tumor in the guise of "variants" and when, on the whole, no general appreciation of the seriousness of certain giant-cell tumors of bone existed. On the other hand, it seems equally clear from the recent literature that some of the pertinent advances of the past 15 years have not as yet been fully assimilated and that even at this late date a good deal of uncertainty still prevails in regard to the clinical and pathologic recognition of genuine giant-cell tumor which must be dispelled before observations in regard to the efficacy of treatment by one method or another are to have much significance.[34]

In 1940 Jaffe, Portis and I attempted to define what should properly be regarded as genuine giant-cell tumor as a basis for more accurate diagnosis and rational therapy In this survey, giant-cell tumor of bone was interpreted as a distinctive neoplasm arising apparently from the nonbone forming supporting connective tissue of the marrow which could be readily identified on the basis of its cytologic details. Specifically it was stated that the tumor was composed of a vascularized network of spindle-shaped or ovoid stromal cells regularly and rather heavily interspersed with multinuclear cells (apparently syncytial stromal cells)

as an integral part of the cytologic pattern. As an important corollary of this study it became evident that genuine giant-cell tumor should be completely divorced from its spurious "variants" with which it had been and to some extent is still confused. As Jaffe[11] has remarked, these so-called variants have little in common, clinically and anatomically with genuine giant-cell tumor and also little in common with *each other except an auspicious prognosis.*

As a result of subsequent detailed investigation of the alleged variants of giant cell tumor, there evolved a clearer concept of these lesions as distinct clinical and pathologic entities in their own right. Thus, the spindle-cell or healing or xanthic variant, so-called was superseded by the rather common lesion now called non-osteogenic fibroma of bone. The *"calcifying or chondromatous giant-cell tumor"* described by Kolodny Ewing, and Codman was reinterpreted and designated benign chondroblastoma of bone[14, 22] in the belief that it represents an independent benign tumor of cartilage forming connective tissue derivation which is unrelated histogenetically to giant-cell tumor of bone. Cognizance should be taken in this connection of the opinion of Willis that a cartilaginous variant of osteoclastoma (giant cell tumor) does exist, although his dissent appears to be based largely upon inferences drawn from a single specimen (labeled "chondromatous osteoclastoma") which, after seeing the sections, I would regard unequivocally as an instance of chondromyxoid fibroma of bone. In another paper dealing with solitary unicameral bone cyst,[17] it was pointed out that, while the lining tissue of a bone cyst might show appreciable giant-cell reaction in fields of blood extravasation, there was no sound basis for postulating any relationship between bone cyst and giant-cell tumor Recently still another rather common pathologic entity frequently mistaken for giant-cell tumor and referred to generally as "atypical, subperiosteal giant-cell tumor in unusual locations" has been clearly delineated under the designation of aneurysmal *bone cyst.*[20] *As for the lesions which Ewing*[7] *in his* last classification of bone tumors (1939) referred to rather vaguely and paradoxically as "certain benign, circumscribed spindle-cell myxosarcomas with few or no giant cells, which run the usual course of giant-cell tumors, it is difficult to trace the reference but altogether con ceivable that the lesions so designated represented instances of the distinctive neoplasm which Jaffe and I[21, 18] have described under the head of chondromyxoid fibroma of bone. Continuing in the same vein, Jaffe[12] has expressed the view that certain tumors in the jawbones of adolescents, which resemble giant-cell tumor cytologically and yet have a uniformly favorable prognosis, may be merely a peculiar expression of reaction to hemorrhage to convey this concept, he has proposed the name "giant-cell reparative granuloma." Bullock and Luck have recently taken up *this idea and have suggested that on occasion comparable changes may ensue* in bones other than the maxilla and mandible ("giant-cell tumorlike lesions of bone") In regard to so-called giant-cell tumors of synovial or tenosynovial tissues, there now seems to be general agreement that such lesions are wholly unrelated to giant-cell tumor of bone. They appear to represent peculiar granulomas rather than true neoplasms, and Jaffe, Sutro, and I[19] have described the condition as such under the head of pigmented villonodular synovitis, bursitis, and tenosynovitis. If one recognizes these distinctions, and they have more than academic import,

then it becomes evident that genuine giant-cell tumor is not nearly as common or as miscellaneous a lesion as was formerly supposed. In fact, on a fair sized orthopedic hospital service, one is not likely to encounter more than 2 or 3 cases a year on the average.

Clinical Features

Age and Sex Incidence.—Our observations have led us to conclude that genuine giant-cell tumor in contrast to some of the alleged variant lesions, is not often observed in patients under the age of 20 years. There are very occasional exceptions to this useful rule it is true (the lower limit of the range of incidence is actually closer to 15 years) but it should be borne in mind that the odds are very much against anyone who ventures a diagnosis of giant-cell tumor in a child or an adolescent, published data to the contrary notwithstanding As for sex incidence there does not appear to be any significant difference (as there is with benign chondroblastoma for example)

Localization.—The great majority of giant-cell tumors develop in the lower end of the femur the upper end of the tibia, and the lower end of the radius (in that order of frequency) Occasional giant-cell tumors are observed also in jaw bones, in the upper end of the humerus, the upper femur the upper end of the fibula, the lower end of the tibia the patella, metacarpal heads, and even phalanges. I have observed relatively few instances in the innominate bone (iliac wing) and in the vertebral column and have never encountered one in a rib, a ✓ clavicle, an ulna, or a bone of the calvarium. Before accepting ostensible giant-cell tumors in such unusual sites, one should require meticulous pathologic verification. Much of the published statistical data, for example, the data cited in 1949 in an editorial in the *Journal of the American Medical Association*[8] apparently culled from the comparatively old article by Christensen,[4] give one a somewhat distorted impression of the incidence and localization of giant-cell tumor particularly in the bones of the upper limb, the skull (exclusive of jawbones) and the pelvis and vertebrae, where, as has been indicated elsewhere,[23] aneurysmal bone cyst is prone to develop.

When a giant-cell tumor is situated in a long bone it usually involves the end of the bone and there are relatively few exceptions to this rule. Willis[31] and some of his British colleagues are inclined to question the validity of this view but it is my impression that they are not as critical as they might be in accepting as giant-cell tumors lesions that develop in the metaphyses of young patients. As noted, such lesions, in the great majority of cases, prove on close histologic scrutiny to be instances of other conditions, on the whole less serious than giant-cell tumor (non-osteogenic fibroma, bone cyst, chondromyxoid fibroma, etc.)

Clinical Complaints.—Like some other tumors of bone, giant-cell tumor develops insidiously and usually has attained appreciable size before its presence is recognized Pain, slight swelling limitation of motion of the neighboring joint, and tenderness on palpation are the complaints that are likely to direct attention to the lesion and point to the necessity for roentgenographic examination. Occasionally infraction of the expanded and attenuated cortical bone overlying the

tumor may provoke exacerbation of symptoms. Pronounced expansion and a sense of crackling of the cortical shell surrounding the lesion are manifestations of a far advanced, neglected tumor that one does not see very often nowadays. In the case of some few giant-cell tumors, one may elicit a sense of pulsation reflecting great vascularity but this finding, too is rather unusual



A. B.

Fig 58—A Roentgenogram of a giant-cell tumor developing in the upper end of a tibia Treatment in this case consisted of thorough curettement. B Roentgenogram of another representative giant-cell tumor situated in the lower end of a femur Fracture occurred at the time of surgery followed by some drainage and delayed healing Six months later it was decided to use roentgen therapy which proved efficaceous (despite the popular admonition against combined treatment) At the follow-up 5 years later the patient was well and doing heavy manual labor

Roentgenographic Appearance

It was formerly thought that giant-cell tumor of bone presented a characteristic multilocular cystlike appearance said to resemble an agglomeration of soap bubbles. As a matter of fact, this appearance is rather unusual for untreated giant-cell

umor and is much more likely to reflect the presence of lesions other than giant cell tumor which grow more slowly permitting the development of reactive grooves and spurs on the endosteal surface of the attenuated cortex overlying the lesions e.g., hemangioma, non-osteogenic fibroma fibrous dysplasia, enchondroma, etc.

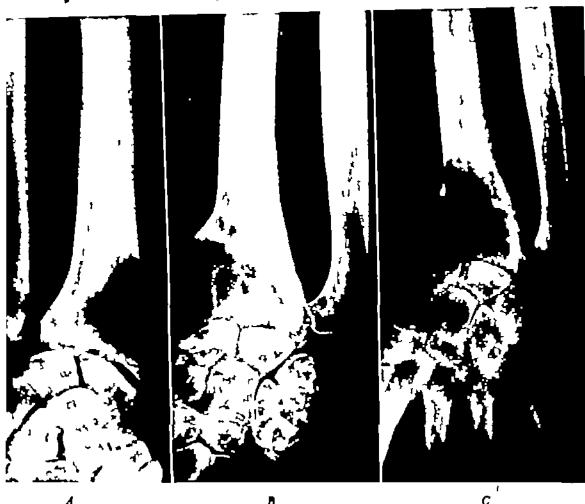


Fig 59.—A series of roentgenograms showing progression of a giant-cell tumor situated in the lower end of a radius, another frequent site of development. *A* Initial film showing eccentric position of the tumor its uniformly rarefied appearance as well as thinning and slight expansion of the overlying cortex which is still intact. *B* The appearance of the tumor 7 months later *C* Its appearance prior to surgical treatment (11 months after the initial film) The tumor now occupies the entire width of the radius and has extended in places through the eroded cortex. The carpal bones show pronounced disuse atrophy The importance of early diagnosis and prompt effective treatment cannot be too strongly emphasized.

Far more important diagnostically are the location of the area of rarefaction in the end of the bone and the thinning and expansion of the cortex, particularly on one side. Another significant point is the practical absence of periosteal new bone formation over the thinned and expanded cortex, not infrequently even where the latter has undergone pathologic fracture. However in the last analysis,

the latter features are not infallible either as roentgenographic guides to the correct diagnosis. Thus, a chondrosarcoma or a fibrosarcoma which has started in an epiphyseal end of a long bone may on occasion produce a roentgen picture closely simulating that of a giant-cell tumor. Further, we have seen cases in which a focus of myeloma did so. The recognition of a giant-cell tumor in sites other than a long tubular bone is likely to present a difficult problem.



Fig. 60.—*A*, Roentgenogram of a giant-cell tumor in the lower end of a femur of a 42 year old man who had complained of pain, slight swelling, and limitation of motion for about 4 months. The tumor was thoroughly curetted (the wall of the cavity was not cauterized, nor were bone chips inserted). On microscopic examination this neoplasm was regarded as a giant-cell tumor of Grade II, that is, as one rather likely to prove aggressive and recur. *B*, Roentgenogram of the recurrent giant-cell tumor 9 months later. (See also Fig. 61.)

Altogether, then, despite the prevailing common opinion, there is *no* set of roentgenographic findings which can safely be regarded as typical of giant-cell tumor of bone. The necessity for reservation as to the diagnosis until a biopsy specimen has been studied is thus apparent. By the same token, the wisdom of the practice of instituting radiation therapy on the strength of a roentgen diagnosis alone, unverified by biopsy, is open to serious question.

Gross Pathology

Inasmuch as most giant-cell tumors are treated, initially at least by curettement or irradiation, it is only occasionally that one has the opportunity to study the gross specimen of an intact tumor unmodified by treatment. Formerly there was no lack of such material since radical excision or amputation of the affected part was freely done as an initial (though late) procedure. Now, all that the pathologist usually sees of the lesion unmodified by treatment is a biopsy fragment or a mass of curettings. Where the lesion has been treated and has recurred, he may subsequently see the entire area involved, but by that time the gross appearance has been greatly modified by such influences as infection and hemorrhage, the effects of radiation, and sometimes even spread of the tumor beyond the limits of the bone.

For information concerning the gross appearance of the natural lesion in its setting the descriptions of Paget, Nélaton, and Gross are still of interest. However these older descriptions usually relate to lesions which, through the very delay of treatment, had been allowed to attain large size, associated with the appearance of pronounced secondary changes. Consequently these descriptions, with their emphasis on extensive necrosis, hemorrhage, cystic softening and the formation of large blood spaces, though accurate as far as very advanced lesions are concerned, do not, on the whole, fit the gross picture of the giant-cell tumor as we see it, now that it is being treated more promptly

I have observed several intact resected tumors in the lower end of the radius and two in the upper end of a fibula The over-all impression one obtains from such specimens is certainly that of a cellular neoplasm. As noted, the tumor involves the end of the bone and the adjacent metaphysis. In the affected area the bone outline is generally found expanded, at least in part. The distended area is usually delimited by a thin shell of bone, over which the periosteum is somewhat thickened. The thin bone shell represents newly formed bone which has replaced the resorbed original cortex. Whatever spongiosa there was originally where the tumor is present has also been resorbed The tumor is often found to have extended to the articular cartilage in one place or another If the bony end plate has been resorbed over any considerable area, the contour of this cartilage may no longer be entirely normal but the cartilage is not likely to be found perforated by tumor tissue. Shaftward this tissue may extend into the major marrow cavity though it is delimited from the marrow by a thin wall of fibrous tissue or bone.

As to the tumor itself its gross appearance naturally depends to a considerable extent on the degree to which it has already undergone the secondary changes mentioned. Tumor tissue which has undergone but little modification is likely to be of a rather uniform dark red or reddish brown color Its more richly cellular areas, however may be gray and of a fleshy consistency, though friable In fact, practically the entire lesion may present this appearance, especially if it is still small. In most specimens, however the color and consistency are found altered by secondary changes which have occurred here and there throughout

The stromal cells are mononuclear and in general resemble young connective tissue cells. They are spindle shaped or ovoid in varying proportions. Correspondingly the nucleus, which occupies much of the cell body is longish or roundish. It contains a moderate amount of chromatin and a more or less central nucleolus. The outlines of the individual stromal cells cannot always be traced completely but it can almost regularly be seen that the cells have cytoplasmic processes. Occasional stromal cells may present evidence of mitotic division The stromal cells of the tumor seem most plausibly explainable as arising through proliferation of the non-osteogenic supporting connective tissue of the marrow



Fig. 63.—*A* and *B* Anteroposterior and lateral views of a giant-cell tumor in the distal tibia which was unusual with respect to location and the youthfulness of the patient (16 years of age) The clinical behavior of the tumor was aggressive, and this was reflected in its cytology (Grade II)

The multinuclear giant cells are found irregularly distributed between the stromal cells. In a given tumor they may be numerous or sparse, and their number may vary from part to part. They are generally from 30 to 60 microns in diameter though sometimes they are 100 microns or even more. In a general way the number of their nuclei increases with the diameter and some of the cells may have many dozens. The nuclei tend to be agglomerated toward the middle

of the cell. They are round or oval, and each has a nucleolus. On the whole, the nuclei of the giant cells are not much different from those of the ovoid stromal cells, and they may even be indistinguishable from them. The cytoplasm of the giant cells is usually considerable in amount and frequently granular and vacuolated. These cells, too apparently have cytoplasmic processes, and some writers have shown that these processes anastomose with those of the stromal cells.

The histologic facts favor the idea that the giant cells and the stromal cells have a common ancestry if indeed the giant cells are not derived from the stromal cells by agglomeration or fusion. On the other hand, they have been regarded by some as megakaryocytes, by some as osteoclasts, and by others as nothing more than agglomerations of wandering phagocytes. Their intimate connection with the walls of vascular channels in many places has led still others to regard them as being of endothelial origin and possibly representing "puffed-up endothelial sprouts" which have migrated between the stromal cells. Some have even contended that the small vascular channels in a giant-cell tumor represent merely canalized giant cells.



Fig. 64—Roentgenogram of a giant-cell tumor in the terminal phalanx of a thumb a rare location for it. This tumor recurred within a year after curettement. The surgeon elected to do a second curettement because he was loath to sacrifice the thumb, but is aware of the necessity for ablation in the event that the tumor recurs again.

In any case the giant cells should not be given the primal position in the genesis of the growth that has been assigned to them by many writers. Doubtless, much of the confusion that exists in regard to the diagnosis and classification of the giant-cell tumor of bone and its supposed variants has resulted from undue emphasis on the giant cells, as well as from the ill advised identification of these cells as osteoclasts. An extreme expression of overemphasis on the giant cells is represented by the untenable theory proposed by Geschickter and Copeland that the giant-cell tumor results from abnormal hyperplasia of osteoclasts left at a site of endochondral ossification. The multinuclear cells of the giant-cell tumor while resembling also show definite differences from indubitable osteoclasts, such as one observes in connection with resorptive and reconstructive processes in a bone site.

The collagenous intercellular material in the giant-cell tumor is most abundant where the stromal cells are very spindly and loosely arranged. Where they are

ovoid and closely packed, the collagenous material is sparse. In relatively unmodified tumor tissue, the blood vessels can be seen as small thin-walled channels lined by flattened cells. Some giant cells are usually seen in intimate relation with the vessel walls. Where there has been hemorrhage into the tumor one finds large vascular sinuses, the walls of which are generally composed of stromal and giant cells. About such areas delicate trabeculae of osteoid may have been laid down. In the vicinity of these regions some free and intracellular blood pigment is usually to be seen. Although it is generally reported that the giant-cell tumor of bone contains at least some lipoid-bearing phagocytes (foam cells) it is only in an occasional instance that they are significantly prominent.

Grading of Giant-Cell Tumors

If one adheres to a strict definition of what should be regarded as giant-cell tumor and strips away all of the alleged variants, so-called, what is left constitutes a formidable neoplasm. The more I see of giant-cell tumors of bone, the more wholesome is my respect for them. Most of them in recent years have been aggressive or potentially aggressive tumors, although one must make allowance for the fact that the tumors that respond well to conservative treatment are not likely to be submitted for consultation. An appreciable number have manifested local recurrence after surgical extirpation, either in the surgical wound or in the operative field after resection. As notable cases among them, I may cite the appearance of *a circumscribed tumor transplant in the surgical wound some months after curettement* of a giant-cell tumor in the upper tibia and in proximity to an extensor tendon sheath after curettement of a tumor in the head of a metacarpal, as well as local recurrence in the soft parts after resection of the head of the fibula and in proximity to a bone graft inserted after resection of the lower end of the radius. In these circumstances, it is difficult and startling to realize that at one time there were those who maintained stoutly that giant-cell tumor did not represent a genuine neoplasm but a tissue reaction to trauma, hemorrhage, or chronic irritation. Altogether it has become increasingly evident that, while giant-cell tumors are not *necessarily* "sarcomas," neither are they *all* "benign" as Bloodgood *maintained. With respect to potential seriousness, they may run the whole gamut from one* extreme to the other. There appears to be substantial agreement, among pathologists at least, that, while many giant-cell tumors are successfully treated by thorough curettement or irradiation, some are undoubtedly aggressive and prone to recur and occasional ones behave like frank sarcomas, either when initially observed or more often, after one or more local recurrences.[34] Obviously statistically valid as well as accurate data reflecting appropriately long follow up records are not readily collected by any single observer. It is my impression, however, as a working hypothesis, that given a sizable group of proved giant-cell tumors, approximately one half are likely to have a favorable outcome if properly treated by whatever method, *approximately one third are likely to prove more aggressive* and recur after treatment (and a considerable proportion of these may eventually come to amputation) while the remaining 15 per cent more or less will be frankly malignant and prone to metastasize to the lungs. An occasional giant-cell tumor will be found to be

malignant on initial tissue examination but more often one has to reckon with malignant changes incidental to one or more local recurrences. Empirical corroboration of this impression comes from the study by Thomson and Turner Warwick (among others) of some 34 giant-cell tumors, 18 of which recurred after local surgical or x ray treatment, and 8 of these in turn eventually proved fatal from metastasis (2 of the sarcomas were associated with Paget's disease)

Along these lines as a guide to therapy and with a view to forecasting prognosis within certain limits, we recommended[14] that giant-cell tumors be subclassified into three grades, arbitrarily designated numerically as I II and III and showing respectively insignificant, moderate, and pronounced atypism of their stromal cells. Willis[31] and also Russell have contended that giant-cell tumors which prove to be aggressive or eventually frankly malignant may not be initially distinguishable from their benign fellows. Similarly Williams, Dahlin, and Ghormley have not found the grading of giant-cell tumors helpful and Jaffe,[12] too, has apparently veered to a position of skepticism (1953) It is true that a giant-cell tumor does not have to be frankly sarcomatous to give rise to aggressive local recurrence or even to metastasize. On the other hand, I find rather consistently that the aggressive and metastasizing tumors are definitely more cellular and show distinctly greater atypism of their stromal cells than the innocuous ones that respond well to conservative treatment (Figs. 66 67 and 68) I can only reiterate that, while no method of appraising potential aggressiveness from cytologic criteria is infallible, in my own experience the grading of giant-cell tumors has proved to be of practical value. Specifically the giant-cell tumors which pursued an aggressive clinical course were, for the most part, tumors of Grade II or II+ rather than Grade I initially while those that eventually became frankly malignant (Grade III) likewise revealed a portent of this ominous tendency in previous tissue specimens. The validity of appraising giant-cell tumors as indicated has also been supported by the findings of Murphy and Ackerman, who have subjected their material to close scrutiny

The tumors falling into the first group (Grade I) which seem to make up about half of any representative series of giant-cell tumors of bone, are those in which the cytologic features indicate the lowest degree of aggressiveness and, hence, a relatively favorable prognosis. The tumors delegated to the other two groups show successively more ominous cytologic features, those of Grade III being definitely malignant. In connection with grading the details of the stromal cells should be closely scrutinized under high magnification, and one should judge the tumor by its most ominous-looking areas rather than by areas selected at random. It follows from this that, for a relatively safe judgment, more material is usually needed than is obtained in a needle or a punch biopsy specimen. In fact, when a mass of curettings is available one should submit a considerable portion of it to cytologic study using particularly the areas least modified by spontaneous secondary changes. Previous irradiation of the growth, too, is likely to be a confusing factor in the grading, since it may have induced fibrosis hyalinization, and calcification as well as distortion and atypism of the stromal cells. Even though it has not been irradiated a recurrent tumor which has become infected may also be somewhat difficult to grade as it tends, on the whole to look somewhat

more ominous than it really is. Nevertheless, allowing for these modifying factors, one can usually still decide with reasonable plausibility on the grade to which a given tumor ought to be assigned.

To belong to Grade I the lesion must show no appreciable atypism of its stromal cells. Though these cells are abundant, they are not densely compacted in a tumor of this grade. In the majority of cases they are predominantly spindle shaped, while in the remainder they are predominantly polygonal or ovoid. Whatever their shape (which does not seem to have any special significance) they are more or less uniform in size. Important also is the fact that one finds in a Grade I giant-cell tumor at most only an occasional stromal cell that has a hyperchromatic or abnormally large nucleus or perhaps two nuclei. A few of the stromal cells, to be sure, may exhibit nuclei in the process of mitotic division, but in any case the mitotic figures are not abnormal. The giant cells are numerous in most fields at least. Their nuclei vary in number, but each cell tends to have a good many of them, and they bear a close resemblance to the nuclei of the stromal cells (Fig 65 *A*)

It should also be noted that a Grade I tumor presents comparatively little evidence of fibrous or collagenous differentiation of its stroma. If present at all, such differentiation is found limited to a few small areas. Indeed, if a lesion of bone exhibits a predominantly fibrous or collagenous stroma that cannot be attributed to previous irradiation, one must be wary of calling it a giant-cell tumor even though the lesion contains a sprinkling of multinuclear giant cells. In addition to not showing much fibrous differentiation, the Grade I tumors present relatively little or no evidence of spontaneous ossification except at their periphery otherwise showing at most a few small trabeculae of new bone. If a lesion under consideration manifests extensive osseous metaplasia, one is dealing, in all likelihood, with something like an osteogenic fibroma rather than with a giant-cell tumor

Some of the Grade I tumors reveal a tendency to microcystic degeneration following hemorrhage or necrosis. However if a lesion in question is essentially cystic, presenting only scattered giant-cell areas in the cyst wall, it again probably does not represent a giant-cell tumor at all but rather a bone cyst containing osteoclasts formed in connection with organization of hemorrhage and resorption of bone.

In regard to the prognosis for the tumors of Grade I it is to be noted that recurrence can be expected in some instances, though not in the majority. Furthermore, in its recurrent state, particularly if it has recurred more than once, a Grade I tumor may finally come to exhibit characteristics which really put it in the next grade.

The tumors of Grade II constitute a somewhat varied group, ranging from those in which the stromal cells show only slight (though definite) atypism to those in which they are strikingly atypical though not yet sufficiently so to justify placing these tumors in the category of the frankly malignant ones. The stromal cells are abundant and closely compacted and may even show plainly an irregular whorled arrangement. In some cases, they tend, on the whole, to be spindle-shaped, though in some areas they may be plumper or ovoid, and an occasional

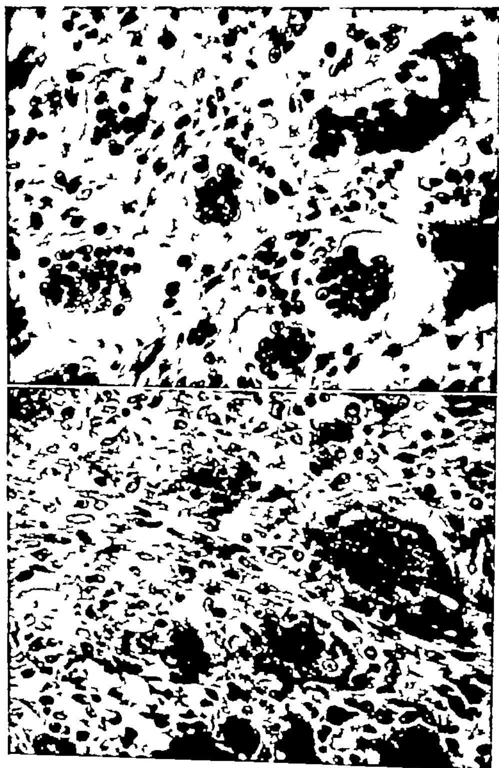


Fig 63-4 Photomicrograph of a representative giant-cell tumor of Grade I, which is most likely to respond satisfactorily to treatment (×420.) *B* A more cellular giant-cell tumor of Grade II This neoplasm developed in the head of a fibula (see Fig 70) and recurred locally following resection. (×420)

cell may even appear anaplastic. At the other extreme there are cases in which the stromal cells are predominantly plump or ovoid, while their nuclei are large and swollen in proportion to the cell as a whole and often exhibit atypism. Specifically in the latter connection the nuclei may vary considerably in size, many of them may be hyperchromatic, and some of them may be multiple, two or three being present in a given cell. In these more ominous cases, in which the lesion may already be considered as potentially malignant, mitotic figures are rather frequently encountered, and some of the latter may appear abnormal (Figs. 65 *B* and 66)

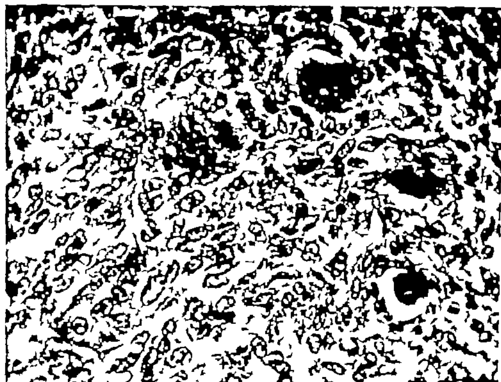


Fig 66.—Another giant-cell tumor of Grade II+ showing more ominous cytology than the neoplasms illustrated in Fig 65 reflected in the swollen pale appearance of its stromal cell nuclei. The giant cells are sparse and contain relatively few nuclei which closely resemble those of the individual stromal cells. This neoplasm developed in the upper end of a tibia (see Fig 71) and 9 months after curettement, a small tumor node recurred in the surgical scar (×420)

In the tumors of Grade II as a whole the fibrillar stroma shows no appreciable tendency toward collagenous differentiation. The giant cells are likely to be abundant in some or in many areas, though they may be sparse in others. Their nuclei may reveal atypism similar in a general way to that of the stromal cell nuclei and running more or less parallel to it. The compacted stroma may be found poorer in vascular channels than it is in the tumors of Grade I While there may be some areas of necrosis, no appreciable tendency toward cystic degeneration is observed. Furthermore the tumors of this grade show no evidence of spontaneous ossification, although an occasional one may show a few scattered osteoid trabeculae.

As to prognosis, it is to be noted that the tumors of Grade II tend strongly toward recurrence and that some of them eventually undergo malignant transformation, although usually it is true only after an interval of some years.

The tumors of Grade III constitute the small group of giant-cell tumors of bone which are frankly and obviously malignant, possessing a sarcomatous type of stroma and a capacity for metastasis. Their stromal cells are abundant and closely compacted and tend to present an irregular whorled arrangement. Their nuclei exhibit atypism almost uniformly and are likely to be unusually large and anaplastic. The giant cells tend to be dwarfed and to contain few nuclei and the latter too, are likely to show atypism (Fig 68)

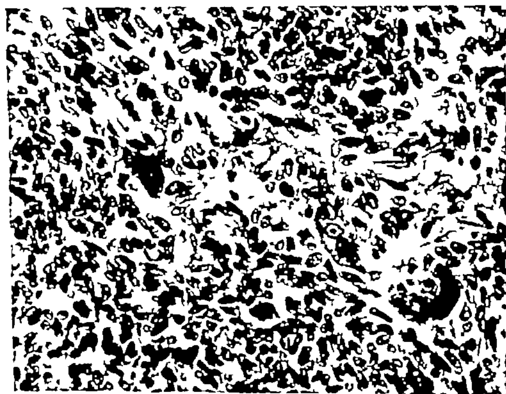
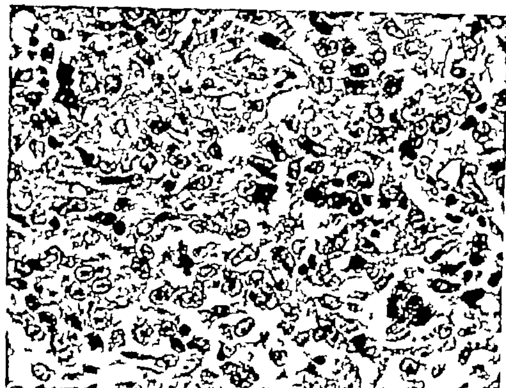


Fig 67—A field of an aggressive giant-cell tumor (in the distal radius, invading the soft tissues) selected to show cellular tracts of plump spindle cells, reminiscent of early fibrosarcoma. Elsewhere, this tumor showed the classical cytology of a giant-cell tumor Grade II+ (on a 1 to 3 scale) (X 420)

Occasionally one encounters a giant-cell tumor which is already frankly sarcomatous when tissue is first taken from it for study More often, however a malignant giant-cell tumor is one which originally belonged to Grade I or II but which has become more and more aggressive in the course of years. Often the increased aggressiveness has followed on repeated curettage, infection, or irradiation, although it is possible that in these cases the malignant tendency of the growth was inherent in it from the beginning The tumors of Grade III metastasize

A



B

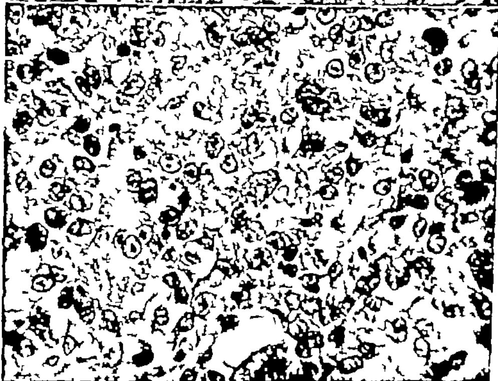


Fig. 68.—*A* and *B* Representative fields of a malignant giant-cell tumor (in a wing of the sacrum) which metastasized widely in spite of deep roentgen therapy Although the architecture of giant-cell tumor is maintained, the stromal cells are compact and distinctly swollen and show significant hyperchromatism as well as an inordinate number of mitotic figures. Compare with Fig 65 which was taken at the same magnification (×420) (Courtesy of Professor Dorothy S. Russell, the London Hospital.)

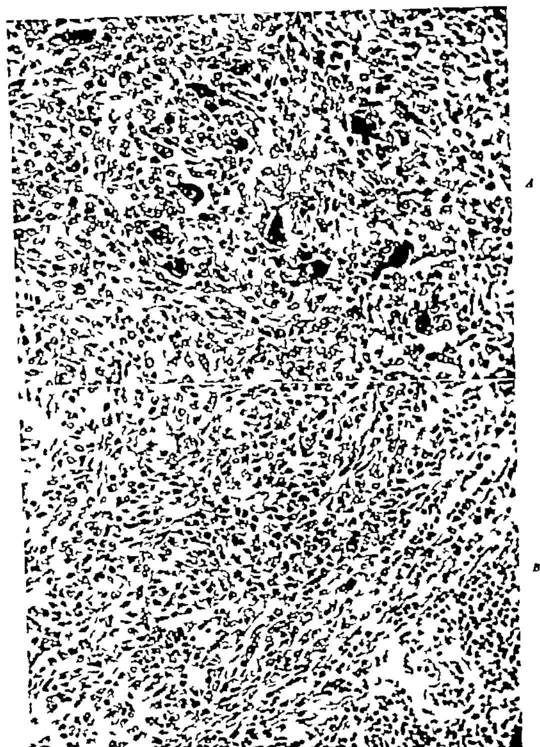


Fig. 69 — *A* Representative field of a pulmonary metastasis of the malignant giant-cell tumor illustrated in Fig. 68, showing a few dwarfed giant-cells within a cellular spindle-cell stroma (×220) *B* From a metastatic node in the spleen of the same case. From this pattern alone, one would hardly suspect that the primary neoplasm was a giant-cell tumor (×220)

sooner or later, particularly to the lungs. In their metastases, at least as I have observed they do not show up as osteogenic sarcoma, if there has been no prior irradiation. In some instances, one can recognize the metastases as those of giant cell tumor although the giant cells may be scant and dwarfed in others, they may look like undifferentiated fibrosarcoma (Fig 69 *A* and *B*)

Problems in Therapy

In regard to therapy generally one finds increasing acceptance, in theory at least, of the basic concept that roentgenographic interpretation alone may be fallacious and that rational treatment must be predicated upon reliable pathologic diagnosis, regardless of whether one favors surgery or x-ray irradiation as the treatment of choice. In the main, however recent contributors have not been overly concerned with pathologic analysis of their material and have been preoccupied with attempting to point out the advantages of x ray therapy over surgical treatment or vice versa. Most of them appear to agree, however that it does not seem to be a good plan to combine the two methods, though precisely why is not clearly indicated. Beyond that, there has been no comprehensive survey of specific problems entailed in the treatment (by either method) of a proved giant-cell tumor that is approached for the first time or of one that has already recurred after treatment. It seems to me that a clear statement of these problems, without prejudice in favor of either modality is the first essential step in the planning of well controlled long range clinical experiments that alone can supply the data upon which a sound therapeutic program must eventually be based.

As indicated biopsy should be resorted to before instituting treatment, irrespective of the method of treatment employed. If one is inclined to favor surgery the diagnosis can be established by conservative but adequate surgical exposure (avoiding pathologic fracture of the attenuated cortex) and frozen section of a bit of representative tissue. There should be no difficulty on frozen section in identifying a giant-cell tumor and in ruling out a sarcoma, although the grading of the tumor may require good paraffin slides. The tumor may then be treated by excision, resection, or thorough curettement, depending upon its location and size. Whenever it is possible to excise or resect the tumor in toto this should be the method selected as the most certain and quickest way to effect a cure (Fig 70) Unfortunately the majority of giant-cell tumors present as relatively large growths in the lower end of the femur or the upper end of the tibia where resection as a routine procedure is hardly feasible, unless one attempts to develop a practical prosthetic device, as Kraft and Levinthal have done. For these, thorough curettement is the procedure generally followed by those committed to surgery In tumors treated successfully by this method, one wonders what happens to residual bits of tumor tissue adhering to the walls of the cavity created by curettement, and can only surmise that they probably undergo necrosis as a result of interference with their blood supply Along the same line of thought, is anything gained by chemical cauterization of the walls of the cavity employing zinc chloride, for example or does this merely impede osseous reconstruction? Also, is

packing of the cavity with bone chips, with a view to hastening osteogenesis, desirable as a routine measure? While most surgeons would answer this latter question in the affirmative their impression is likely to be largely subjective. (In regard to the desirability of employing supplementary irradiation directed against any residual tumor that may be present, the statement is made in the editorial



A. *B.*

Fig 70—*A* Roentgenogram of a giant-cell tumor developing in the upper end of a fibula (its cytology is illustrated in Fig 63 *B*) This patient was only 17 years of age—one of the few exceptions to the rule that giant-cell tumor is distinctly unusual below the age of 20 years. *B* Roentgenogram of the resected upper end of the fibula showing the giant-cell tumor illustrated in *A* Sections revealed that the neoplasm had extended through the expanded cortical shell in places into the contiguous muscle tissue. Within several months, local excision of recurrent tumor became necessary but the patient has remained well for the past 3½ years.

previously cited[8] from the *Journal of the American Medical Association* that "irradiation as an adjuvant to curettage may apparently stimulate recurrence or increase the aggressiveness of the lesion.") While this contention undoubtedly echoes a large section of current opinion, actually what proof is there of its validity? And if the suggested hazard is real, does it apply to small or moderate as well as to large doses of x ray?) Still another suggested approach about which one must

A

B

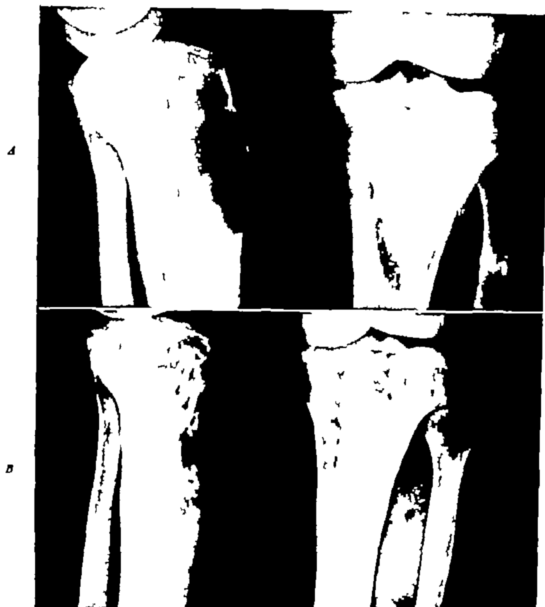


Fig. 71 —*A* and *B* Roentgenograms of another giant-cell tumor in the upper end of a tibia taken before and after thorough curettement and packing with bone chips Complaints referable to the neoplasm had been noted for about one year The cytology of this tumor is illustrated in Fig 68 Although limited biopsy of the previously curetted area failed to reveal the presence of recurrent tumor this case will bear close watching and may eventually come to amputation. About 1 year after surgery a localized tumor node appeared in the subcutaneous tissue in the line of the surgical scar and was excised. Recurrence of giant-cell tumor in the upper tibia was noted 3½ years after the initial curettement. It was decided to do a thorough curettement once again, and the patient has remained well to date.

keep an open mind is the use of limited x-ray irradiation prior to curettement, as advocated by Haggard and Hare. (These authors claim that such preliminary irradiation, adequate to arrest tumor growth temporarily yet not intense enough to induce bone necrosis or prevent soft tissue healing renders the tumor tissue sufficiently firm and avascular to permit really thorough curettement.)

If one is committed to x ray irradiation of giant-cell tumor by choice, then sufficient tissue for diagnosis can still be obtained by resorting to aspiration or drill biopsy repeated if necessary in the event that the initial specimen is inadequate or inconclusive. Most radiotherapists freely admit, off the record at least, that



Fig 72.—Roentgenogram of a previously irradiated giant-cell tumor in the upper end of a tibia. It is noteworthy that biopsy performed 7 years after treatment revealed the presence of residual giant-cell tumor tissue. This was distinctly modified by irradiation and impregnated by foam cells in places, but was still viable.

roentgen interpretation alone has its inherent limitations, Brailsford to the contrary notwithstanding, and that accurate pathologic diagnosis prior to treatment is eminently desirable. They readily concede, on the one hand, that bone lesions less serious than giant-cell tumor may simulate the latter roentgenographically and on the other hand, that occasionally malignant tumors of one kind or another may not be readily distinguishable from giant-cell tumor if one has to rely solely on the roentgenogram. Unfortunately some of these radiotherapists appear content to pay lip service to the principle involved, while others resort to biopsies but are willing to accept casual impressions, being themselves unaware of the subtleties in differential diagnosis that confront the pathologist. There seems to be good reason to

hold empirically that x ray irradiation per se is capable of effectively controlling a certain number of giant-cell tumors, particularly the less aggressive ones. In the absence, however of acceptable proof of the pathologic identity of the lesions treated, claims for the efficacy of such treatment lack scientific validity despite long range follow-up observations. To my knowledge, a well-controlled and altogether convincing sizable series of giant-cell tumors treated by roentgen therapy and followed for 5 to 10 years has yet to be presented.

This tendency to casual empiricism is further reflected in the fact that no unanimity of opinion seems to exist among the exponents of roentgen therapy in regard to the optimum tumor dose that should be employed or the manner in which it should be administered. Thus, some contend that a total tumor dose as small as 1 000 r suffices to effect a cure, others are inclined to administer as much as 2,000 or 3 000 r while still others employ doses considerably in excess of 3 000 r *in spite of the demonstrated hazard that some patients so treated may manifest the* development of sarcoma in the lesion following a latent interval of 5 or more years after irradiation. I have personal knowledge of several cases in point in which sarcoma developed within an irradiated and ostensibly cured giant-cell tumor after a long latent interval, and Cahan, Woodard, Higinbotham, Stewart and Coley[3] have reported several others in connection with a general survey of sarcoma in irradiated bone. Three additional instances in point were recorded recently by Cruz, Coley and Stewart.[8] Such cases are not very common in relation to the total number irradiated, but they are sufficiently numerous to indicate that bone lesions cannot be irradiated with very large doses of x ray with impunity The practical importance of these observations is that, if one elects to irradiate a giant-cell tumor one should use the smallest possible effective tumor dose, i.e. if 1 000 r will suffice, avoid using 3 000 r or more.

The effective control of a giant-cell tumor which has already recurred locally following treatment, whether curettement or irradiation, raises still another set of problems that require some clarification In the event that the initial therapy has been surgical, what is the likelihood that re-curettement will effect a cure? If one is tempted to employ irradiation rather than further surgery one runs counter to the popular admonition that combined treatment leads to generally unsatisfactory results. It may be true that roentgen therapy for a tumor which has recurred following curettement is not as effective as one might wish, but are the failures necessarily attributable to combined treatment? May they not indicate merely that irradiation is not nearly as effective against the aggressive giant-cell tumors of Grade II as it is against the more favorable tumors of Grade I? Before one categorically condemns combined therapy in such cases one must, in all fairness, compare the follow up results with those in which re-curettement has been employed for recurrence

In the event that the recurrent tumor has been initially treated by roentgen therapy in presumably adequate dosage, what is the likelihood that a second course of irradiation to the limit of tolerance will be any more effective? In so far as the feasibility of supplementary surgery is concerned one can readily appreciate the hazards of failure of tissue healing and of infection entailed in the curettement

of irradiated tissues, but are these necessarily a deterrent in dealing with tumors which have received only moderate doses of x ray and precisely what is the limit of tolerance? If neither of these alternatives seems attractive, should one advocate surgical ablation for giant-cell tumors that have recurred in spite of what seemed to be adequate irradiation? As Coley[3] has remarked, "There are few situations in the entire field of bone tumors which afford greater anxiety or which tax the judgment and intuition of the professional adviser more sorely than these cases of giant cell tumor which fail to yield to radiation therapy." I do not presume to have the answers to the questions raised, but I submit that, notwithstanding all that has been written on the subject of giant-cell tumor to date, there are still basic problems in therapy that require renewed consideration and cannot be circumvented by facile generalizations.

In dealing with a giant-cell tumor which has recurred more than once, I am firmly of the opinion that ablation should be resorted to if the tumor is in a surgically accessible site, since to temporize further is to invite frank malignant change and pulmonary metastasis. In reading the published case reports on malignant giant-cell tumors one cannot fail to be impressed by the fact that in these cases amputation was resorted to much too late to be effective.

Summary

Giant-cell tumor of bone is a distinctive neoplasm arising apparently from the nonbone-forming, supporting connective tissue of the marrow, which can be readily identified on the basis of its cytologic details. The tumor is composed, cytologically of a vascularized network of spindle-shaped or ovoid stromal cells, regularly and rather heavily interspersed with multinuclear cells (apparently syncytial stromal cells) as an integral part of the cytologic pattern. Giant-cell tumor so conceived is not nearly as common or as miscellaneous a lesion as has been supposed in the past. It must be clearly distinguished from the brown tumors so-called of advanced hyperparathyroidism, from most epulides, and from a variety of other less serious tumors of bone formerly associated with giant-cell tumor in the guise of "variants." Among the latter are such distinctive lesions as non osteogenic fibroma, benign chondroblastoma, solitary unicameral bone cyst, aneurysmal bone cyst, and chondromyxoid fibroma of bone. They have little in common, clinically and anatomically with genuine giant-cell tumor and little in common with each other except a uniformly favorable prognosis. Until these distinctions are clearly and generally recognized, observations in regard to the efficacy of treatment by one method or another will continue to have but limited significance.

If one adheres to a strict definition of what should be regarded as giant-cell tumor and strips away all of the alleged variants, so-called, then what is left constitutes a formidable neoplasm to be reckoned with. With respect to potential seriousness, giant-cell tumors range the whole gamut from those that respond satisfactorily to well-conceived treatment, through those that are more aggressive and prone to recur locally to those that may eventually become sarcomatous and metastasize. Along these lines, as a guide to therapy and with a view to forecasting

prognosis within certain limits, it is advocated that giant-cell tumors be graded I II, or III according to whether they show insignificant, moderate, or pronounced atypism of their stromal cells. In regard to therapy I have surveyed some of the specific problems entailed in the treatment, by either surgery or irradiation, of a giant-cell tumor that is approached for the first time, and of one that has already recurred after treatment.

From the clinical point of view it is helpful in differential diagnosis to bear in mind that genuine giant-cell tumor is not likely to develop in patients under the age of 20 years. Also despite the opinion of some, there is no such thing as a typical or characteristic roentgen picture of a giant-cell tumor By the same token, the necessity for establishing accurate pathologic diagnosis before instituting treatment, whether surgical or irradiation, cannot be too strongly emphasized.

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XII

Tumors of Bone of Vascular Origin

Hemangioma, Hemangio-Endothelioma,

Hemangiopericytoma (Glomus)

Hemangioma

Although hemangioma in general represents a fairly common neoplasm, the occurrence of benign vascular tumors within bone is rather unusual at least in the sense of clinically or roentgenographically evident lesions constituting a surgical problem. Thus, Watson and McCarthy in reviewing a series of over 1 000 cases of vascular tumors of all types treated at Memorial Hospital, found only 5 that originated within bone. Of these, 3 were encountered within a lumbar vertebral body 1 in a rib and 1 in a mandible. *This is in keeping with my experience.* In the course of the past 15 years, I have had occasion to observe a mere handful of hemangiomas of bone as surgical specimens.

Such solitary localized tumors must be distinguished, however from the not too uncommon instances in which hemangioma formation in portions of one or more bones may be observed in association with comparable involvement of the contiguous soft parts (in a hypertrophied lower extremity for example) as an integral part of a developmental anomaly of hemangiomatosis. These unusual expressions of hemangiomatosis may be manifested by involvement of the bones of one region (such as the knee as in a case I saw recently in which the proximal tibia and fibula and patella were affected) of an entire limb or of a major part of the skeleton, tending to produce a striking degree of osteoporosis. Cognizance must also be taken of comparable rare instances of lymphangiomatosis of bone, with or without associated involvement of the soft parts of the affected extremities.

According to Sherman, who surveyed some 60 cases of hemangioma of bone recorded in the literature fully two-thirds were located in the skull or vertebral column, approximately one fourth in the long bones and the remainder in such sites as the innominate bones, the tarsal bones and the scapula. A comprehensive discussion of hemangiomas of the skull, in particular is to be found in a recent paper by Wyke dealing with some 40 recorded cases. These developed most often in the parietal and frontal bones and were encountered for the most part in adults past 30 years of age and especially in women. Roentgenographically as Wyke and



Fig. 3 —Roentgenogram showing a small circumscribed, lytic defect in the frontal bone of the calvarium which proved to be a hemangioma (see Fig 5)

others[3] have pointed out, a hemangioma of the calvarium is likely to present as a circumscribed, round or oval, honeycombed area of rarefaction, tending to bulge the outer table. If the lesion is visualized in tangential views, another rather characteristic feature may be demonstrated namely, the so-called "sun ray" appearance produced apparently by fine spicules of reactive new bone radiating from the center of the lesion. It should be noted, however by way of differential diagnosis, that these striations do not all have a perpendicular orientation, such as one may observe when the calvarium reacts to the presence of an underlying

eroding meningioma. On surgical exploration, a hemangioma of a calvarial bone presents as a hard, blue-domed lump lying beneath the intact pericranium. Histologically its pattern may be either capillary or cavernous. In regard to prognosis, it is pertinent to note that in none of the cases surveyed by Wyke was there any indication of malignant change. Well illustrated pathologic data of value in regard to hemangiomas of the skull specifically may be found in a recent paper by Kleinsasser and Albrecht.[13]



Fig 74.—Another hemangioma of a frontal bone showing the so-called sunburst effect which would lead one to suspect the diagnosis before surgery

Hemangiomas of vertebral bodies are said to be fairly common, and the anatomic studies of Töpfer have been repeatedly cited to the effect that pertinent lesions in vertebrae held to represent hemangiomas were found in approximately 12 per cent of over 2,000 subjects examined at autopsy It is significant, however that in none of these cases had the lesions in question provoked any clinical symptoms, or been recognized roentgenographically It is true that one occasionally encounters, as a fortuitous finding at autopsy the presence of a circumscribed

roundish bright red hemangioma like focus within the spongiosa of a vertebral body commonly a dorsal or a lumbar body Such foci usually measure up to 1 to 2 cm *in greatest diameter and are found on microscopic* examination to represent a congeries of closely approximated thin walled, dilated and engorged blood vessels, apparently venules and capillaries. They are not at all discernible roentgenographically even in roentgenograms of specimens which afford great clarity of detail. Further in sections of such lesions one fails to observe any significant alteration of the surrounding bone. It has always seemed to me that such vascularized foci may reflect nothing more than localized venous stasis, and as such, hardly represent hemangiomas in the sense of a neoplasm any more than an esophageal varix or a plexus of dilated hemorrhoidal veins constitutes a tumor of blood vessels.

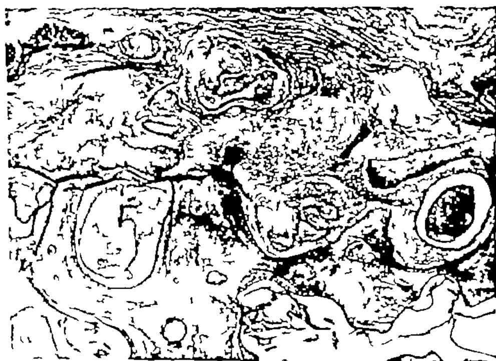


Fig 5—Photomicrograph of the hemangioma (of a frontal bone) illustrated in Fig 73 The overlying periosteal connective tissue is also permeated by numerous prominent blood vessels. (×85.)

In regard to clinically significant lesions reported as hemangiomas of the spine, it is relevant to point out that a certain number of them, at least, particularly those which have produced prominent expansion of the neural arch and perhaps part of the adjacent body of one or two contiguous vertebrae, may actually represent instances of aneurysmal bone cyst. In this connection, also it perhaps needs to be emphasized that in general, an unverified roentgen diagnosis of hemangioma of a vertebral body may not be too trustworthy I recall a pertinent instance in which a peculiar rarefied and expanded lesion in a lumbar body was irradiated without prior needle biopsy on the premise that it represented a hemangioma, and it was not

until 2½ years later that it became quite evident that the lesion in question actually was an initially solitary focus of myeloma. It is not intended to convey the impression, however that bona fide hemangiomas of vertebrae do not exist, but they are probably no more frequent there than they are in the calvarium. As Bucy and Capp have emphasized roentgenographically discernible hemangiomas of the spine are likely to present a distinctive, vertically striated appearance, and it is not unusual for them to involve two or more contiguous bodies (Fig 76) They may come to clinical attention because of symptoms of pressure on the spinal



Fig. 76.—Roentgenogram showing the vertical striated effect commonly held to be associated with hemangiomas of vertebral bodies.

cord or its nerve roots. For their effective control, it does not appear necessary to resort to hazardous laminectomy and high voltage roentgen therapy has been recommended by Watson and McCarthy as the treatment of choice, affording complete relief of symptoms.

In a flat bone, such as a rib a hemangioma may give rise to a symmetrical, fusiform expanded lesion presenting pronounced thinning of its distended cortex, without appreciable periosteal new bone reaction. The "sunburst" effect charac-

terizing hemangioma in some other sites may be inconspicuous or entirely lacking, and one may observe instead a trabeculated or honeycombed pattern A pertinent instance of this kind has been reported recently by Dorner and Marcy, in which the expanded cortical shell at the site of rib involvement was found to contain soft reddish tumor tissue. The latter on microscopic examination, was characterized by the presence of a meshwork of large, engorged thin walled blood vessels indicative of a cavernous hemangioma. A hemangioma in a foot bone may like

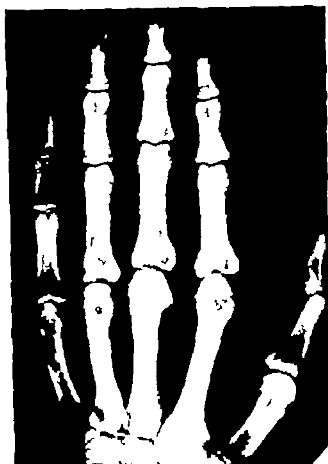


Fig 77—Roentgenogram of a hand showing multiple sharply punched-out, rarefied defects in the third and fifth fingers reflecting the presence of hemangio-endotheliomas. (The largest one in the distal phalanx of the fifth finger was biopsied.) The patient also presented a small hemangio-endothelioma in the subcutaneous tissue of the wrist.

wise present a pseudotrabeculated "soap bubble" appearance roentgenographically and I have observed a pertinent instance in an os calcis, which was regarded as a probable giant-cell tumor prior to surgical exploration. This lesion was curetted and packed with bone chips and went on to uneventful healing (Fig 78 A)

As for hemangiomas in long bones, the relatively few recorded instances indicate that here also, hemangioma may give rise to fusiform or more localized expansion of the affected bone, often the end of the bone, as well as pronounced thinning



Fig. 78.—*A*, Photomicrograph of a representative field of a capillary hemangioma which developed within a calcaneus and presented a well-circumscribed, pseudotrabeculated appearance roentgenographically. Though curettement of the lesion and packing of the defect with bone chips effected a clinical cure. *B*, Photomicrograph of hemangio-endothelioma of an ischium. (×100.)

of the overlying cortex without necessarily provoking appreciable periosteal reaction. Roentgenographically such lesions are likely to present a rather distinctive, coarsely loculated or honeycombed rarefied appearance that may suggest hemangioma, if one is alert to the possibility. Acceptable accounts of hemangiomas of limb bones (along with some others which seem clearly to deal with hemangio-endotheliomas, though labeled hemangiomas) may be found in papers by Hitzrot, Sherman, Thomas, and Geschickter and Maseritz, among others.



Fig. 79.—Roentgenogram of a small, well-circumscribed rarefied lesion in the pubic bone of a child which was curetted and found to represent a hemangioma. The slight periosteal new bone apposition observed on the superior border of the defect had caused some concern. The rather nondescript appearance of a lesion such as this would scarcely permit one to suspect the correct diagnosis preoperatively.

Hemangio-Endothelioma

Malignant tumors of blood vessels are quite rare in general, and this is particularly true of those arising within bone. Furthermore, not all of the recorded tumors interpreted as malignant tumors of vascular origin are acceptable as such. It seems clear that some actually represent vascular neoplasms of other kinds, while the reports of some others are too vague or equivocal as to essential details to permit of reliable classification. Altogether too few observers have resorted to silver staining to establish clearly the presence of atypical endothelia in relation to obscured vascular sheaths, or the presence of free vascular anastomoses. In particular it is pertinent to note that the tumors classified by Ewing in his text as angio-endotheliomas and also reported as such by others,[16] have a striking resemblance to clear-cell renal carcinoma which, as is well known, may give rise to solitary skeletal metastasis, notably in the humerus. On the other hand, some of the cases reported as hemangioma of bone have obviously been underdiagnosed, as noted, and seem

actually to represent instances of malignant hemangio-endothelioma to judge by the illustrative photomicrographs. In regard to nomenclature, also, the use of such terms as angioblastoma and angiosarcoma, as well as telangiectatic sarcoma and malignant bone aneurysm, to denote obviously malignant tumors featuring blood vessel formation, has further contributed to confusion, and I am inclined to follow the suggestion of Stout that all the genuine malignant tumors of vascular origin, except for the aggressive or metastasizing *hemangiopericytomas*, be *grouped under* the single head of malignant hemangio-endothelioma. On the whole, as Stout has emphasized, these are extremely malignant tumors which often have already extended by hematogenous spread before they are recognized.



Fig. 80.—Photomicrograph of a field of a malignant hemangio-endothelioma showing an intravascular vasoformative tumor thrombus. This neoplasm developed in an iliac bone of a 22 year old man and metastasized to a rib despite local resection. (×65)

The foregoing reservations notwithstanding, a number of well-documented cases of malignant hemangio-endothelioma of bone have been recorded by Fienberg and Baehr Thomas Geschickter and Maseritz, and Stout, among others. The tumors cited were all malignant when first observed and I have no knowledge of any hemangio-endothelioma that developed through malignant change in a benign hemangioma. The first mentioned authors have reported a pertinent tumor arising in the tibia, which manifested its aggressiveness by extension to the popliteal artery. Thomas, in a survey of the relevant material of the Bone Sarcoma Registry cites an instance of a recurrent malignant hemangio-endothelioma (designated as

angiosarcoma"), involving a number of tarsal bones. Stout,[31] in a comprehensive discussion of some 18 collected cases of hemangio-endothelioma in general included 2 malignant neoplasms which originated in bone. The first of these, encountered in a 60-year-old woman, involved the lower ends of the tibia and fibula. Roentgenograms of the affected bones showed destruction, rarefaction and widening and at surgical exploration these were found to be filled with very vascular tissue and to resemble sponge rubber in the gross. Roentgenograms taken 3 months later revealed further extension of tumor locally as well as a suggestive area of involvement in the greater trochanter of the femur on the same side. The second pertinent tumor reported by Stout developed in a rib of a 20-year-old woman and metastasized widely proving fatal within 2 or 3 years. On histologic examination this neoplasm showed, in some areas, vascular tubes lined by elongated cells in other areas, rounded and heaped up endothelia and in still other fields, overproduction of tumor cells in solid masses tending to obscure the vascular tubes. Gordon Taylor and Wiles have rendered a brief but interesting clinical account of a pulsating hemangio-endothelioma of an iliac bone, over which a to-and fro murmur was audible. It was elected to do a hindquarter amputation in this case. Pollak has reported an instance of a frankly malignant hemangio-endothelioma of the sternum, which metastasized to the calvarium and a humerus, and proved fatal shortly thereafter, despite radical local resection and heavy x ray irradiation. It is pertinent to note that in neither of the 2 foregoing cases were the roentgenograms sufficiently distinctive to suggest the diagnosis prior to surgical exploration. An extraordinary instance of hemangio-endothelioma manifesting symmetrical involvement of both upper femora and progressive extension into the contiguous innominate bone has been reported by Hauser and Constant. In this case, as in a number of others just cited, embarrassing hemorrhage from soft, friable, richly vascular tumor tissue was encountered at biopsy. It is noteworthy that this patient had survived for 9 years without evident metastasis, even though the tumor in the interim had come to fill most of the pelvis.

I have also observed a malignant hemangio-endothelioma of an iliac bone (in a young man 22 years of age) the roentgenograms of which were originally thought to suggest the presence of a chondrosarcoma. At exploration, the neoplasm was found to be composed of hemorrhagic, friable tumor tissue which was extending into the adjacent muscle. Sections showed that the tumor cells were freely invading blood vessels and flourishing as remarkable intravascular vasoformative tumor thrombi, so that it came as no great surprise when metastasis to a rib was noted some months later in spite of resection of the primary growth (Fig 80). In summary then, malignant hemangio-endotheliomas of bone are comparatively rare neoplasms which are seldom identified clinically and roentgenographically prior to surgical exploration, and which, on the whole, are likely to be so aggressive or so far advanced by the time they are recognized as to have a serious prognosis despite radical surgery.

Hemangiopericytoma (Glomus)

We are concerned here mainly with the glomus tumor which Stout and Murray regard as the most highly organized expression of the neoplasm they have

none of which were any stigmas of generalized neurofibromatosis observed. The first of these, reported by Gross, Bailey and Jacox, deals with a neurilemoma of the shaft of a humerus in a woman 30 years of age, who had been aware of an aching lump on her arm for about 3 years. Roentgenograms revealed a well-outlined, though rather nondescript, ovoid area of rarefaction, with some erosion also of the contiguous cortex and periosteal new bone apposition at the lower angle of the lesion. At exploration, a soft, fleshy slightly fasciculated, ovoid, well encapsulated tumor about 2 by 1 by 1 cm., was found at the site indicated, apparently arising in the interior of the bone. Microscopically, the tumor presented a palisaded architecture, as seen commonly in neurilemomas of peripheral nerve

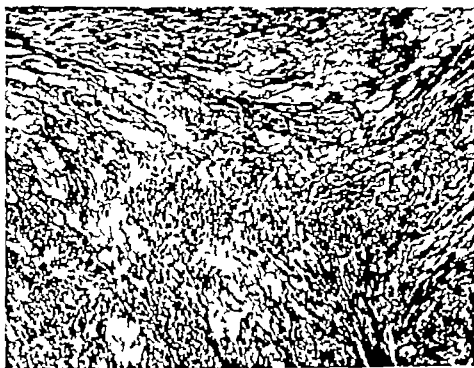


Fig 81—Photomicrograph of a representative field of a small circumscribed tumor within a patella, which was interpreted as a neurilemoma. Such tumors are rarely encountered in bone, as noted.

sheaths, although the authors designated the tumor as a neurofibroma. Another case, reported by DeSanto and Burgess, deals with a comparable tumor in the mid shaft of an ulna of a man of 37 years, who, interestingly enough, had sustained no fewer than 5 pathologic fractures over a period of 8 years, before the lesion was resected It is interesting to note also that the tumor was not particularly painful. The initial x ray picture showed a somewhat eccentric, hemispherical area of rarefaction with localized expansion of its cortical contour At surgery it was noted that the tumor appeared to arise from, and grow out of the shaft of the ulna, and the illustrative photomicrographs leave no doubt that it was a typical neurilem

oma. The same authors also described an unusual instance of an neurilemoma arising from the dorsal root of the fifth lumbar nerve and invading the right sacral wing secondarily producing a large irregular defect in the first and second sacral segments. This tumor though comparatively large for a neurilemoma (6 by 4 cm.) was circumscribed, and the authors emphasize that bone erosion is not per se indicative of malignancy On the other hand it is possible for such tumors to be malignant, and I recall a remarkable autopsy specimen of a spine which showed erosion of a number of vertebral bodies by malignant Schwannomas developing in a case of Recklinghausen's neurofibromatosis.

Apropos of neurilemoma of bone also I have observed another pertinent instance of a small circumscribed surgically extirpated tumor developing within a patella, the whorled palisaded histologic pattern of which was clearly that of a nerve sheath tumor (Fig 84) Still another beautifully illustrated and well-documented case is that reported by Jones, dealing with a neurilemoma of a metacarpal bone. The involved bone area was resected and a graft used for reconstruction, with a good functional result.

In regard to malignant Schwannoma of bone, one of the few well-documented relevant accounts that I can find in the literature is that of Peers. This deals with a tumor in a 55-year-old man, situated again in the mid-shaft of a long bone (an ulna) which was labeled as a primary intramedullary neurogenic sarcoma (perineural fibroblastoma) The cytology of this tumor seems clearly to establish its Schwannian character Amputation was performed in the belief that it was malignant, and the follow up did not extend beyond 20 months. Another comparable instance is that reported by Güthert of a malignant neurinoma in the mid-shaft of a humerus of a young man 20 years of age The tumor was comparatively small, but had extended *through a cortical perforation into the* contiguous soft *parts, so that it* was deemed necessary to amputate the affected limb Many fields of the tumor were still clearly recognizable as neurinoma microscopically

With respect to nomenclature, and, in particular with regard to the use of the term "neurogenic sarcoma," it is relevant to cite the conviction of Stout[14, 15] that this term is ill conceived and should be abandoned as confusing and obstructive. He maintains rather forcefully that tumors called neurogenic sarcoma (if they are not fibrosarcomas starting from fascial and other tissues outside the nerve and secondarily involving it) are actually malignant Schwannomas and should be so designated. According to this view there is no sound basis for the supposition that there is a special variety of nerve fibrosarcoma that can be designated as "neurogenic sarcoma."

The paucity in the literature of malignant Schwannomas arising in bone is somewhat puzzling, although it is possible that such neoplasms go unrecognized for the most part, as Stout points out, through unfamiliarity with the remarkable potentiality of Schwannian cells, which by metaplasia are said to be capable of producing a wide variety of tissues (cartilage, bone, fat, striated muscle etc.) not ordinarily thought of as being derived from them. Obviously this consideration raises many subtle problems in differential diagnosis and, unfortunately most pathologists do not have facilities for tissue culture studies at their disposal.

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XIV

Chondrosarcoma of Bone

Until comparatively recently the basic differences between chondrosarcoma and osteogenic sarcoma were not generally appreciated, and there was a tendency to lump together cases of chondrosarcoma (and also of central fibrosarcoma) along with genuine instances of osteogenic sarcoma. One still finds certain neoplasms indiscriminately labelled as osteochondrosarcoma or chondro-osteosarcoma, although this practise is no longer common. Actually there are relatively few tumors in point which do not permit a clear and sharp distinction (these are mainly rather primitive sarcomas occurring in children) On a clinical level one still finds published analyses of follow-up data bearing on the 5 year survival rate in osteogenic sarcoma, in which the relatively favorable outcome clearly reflects the inclusion in the clinical material studied of an appreciable number of cases of chondrosarcoma (as well as of other lesions less serious than osteogenic sarcoma) The insistence upon the clear separation of chondrosarcoma and osteogenic sarcoma is by no means an academic point. It has a firm pathologic basis and, as intimated, is important clinically in so far as treatment and prognosis are concerned. Phemister was among the first to stress the need for this distinction. The Committee of the Registry of Bone Sarcoma in its revised classification of bone tumors (1939) likewise advocated that chondrosarcoma be separated from *osteogenic sarcoma as a distinct category*

In regard to significant clinical differences between the two neoplasms, it is pertinent to note that chondrosarcoma is distinctly less common. Also it usually appears at a much later age, except in comparison with osteogenic sarcoma complicating Paget's disease of bone. Moreover chondrosarcoma ordinarily pursues a much slower course, not metastasizing to the lungs for years, while osteogenic sarcoma has often already metastasized by the time it is recognized as such (even though x ray films of the chest may still appear negative)

The basic anatomic difference between the two lesions is that chondrosarcoma develops out of full-fledged cartilage while osteogenic sarcoma issues from more primitive tissue developing out of bone forming mesenchyme. Ordinarily in an osteogenic sarcoma, most of the *proliferating connective tissue, which may be*



A



B

C

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Fig. 88.—*A* Roentgenogram of another peripheral chondrosarcoma which developed originally from the cartilage cap of an osteochondroma on the upper shaft of the humerus. The picture illustrated represents its third recurrence after surgical removal over a period of about 10 years. Despite the ominous impression created by the roentgenogram it was possible to extirpate the neoplasm completely without resorting to radical resection. *B* Photograph (appreciably reduced) of a representative slice of the peripheral chondrosarcoma illustrated in *A*. The tumor is composed of facets of whitish hyaline cartilage showing focal areas of softening, as well as calcification. *C* Photomicrograph of a field showing a cartilage cell with two plump nuclei (×250)

quite anaplastic, becomes converted into neoplastic osteoid tissue and bone directly though it usually also forms some neoplastic cartilage, which in turn tends to undergo rapid calcification and ossification. In an occasional osteogenic sarcoma, osteogenesis may even proceed predominantly via the cartilage stage, and cartilage may thus be a prominent feature in the histologic composition of the lesion. However, even in such an osteogenic sarcoma, if one does not limit one's scrutiny to a small field of the tumor and particularly to the periphery of it, one will also see that in other places the basic proliferating connective tissue is merging directly into neoplastic osteoid tissue and bone. On the other hand, in a chondrosarcoma, though large areas of the hyaline matrix may have become myxomatous or even calcified and ossified, the basic proliferating tissue of the tumor is full-fledged cartilage. In contrast to osteogenic sarcoma, properly so-called, chondrosarcoma never shows neoplastic osteoid tissue and bone *evolving directly from a sarcomatous stroma.* These general and anatomic differences constitute an adequate foundation for distinction between osteogenic sarcoma and chondrosarcoma of bone.

There was a tendency in the past [1,4,5,6,9] to underrate the potential seriousness of actively growing cartilage tumors until their aggressive clinical behavior could no longer be ignored or until their histologic picture (as seen in surgical specimens) had become crudely and obviously sarcomatous. At this stage, unfortunately the chances for cure, even by drastic measures, may be sharply reduced. As we showed [10] in 1943 subtle but telltale histologic indications of malignant change are already present even in the early stage of the evolution of a chondrosarcoma. They may have to be searched for particularly in an early lesion but in any case they can be recognized if adequate material is examined and proper significance attached to relatively inconspicuous cytologic abnormalities. Keiller in 1925 pointed out clearly the importance of attention to details regarding the cells (and particularly the cell nuclei) as a means of distinguishing between benign and malignant cartilage growths. Our own experience has taught us that a cartilage tumor is no longer to be regarded as benign if when viable noncalcifying areas are examined it shows, even in scattered fields (1) many cells with plump nuclei (2) more than an occasional cell with two such nuclei and especially (3) giant cartilage cells with large single or multiple nuclei or with clumps of chromatin The importance of making the correct diagnosis early resides in the relative amenability of chondrosarcomas in accessible sites to early radical surgical treatment (Figs. 100 and 101) The criteria indicated have gained wide empirical acceptance and their validity has been supported by the observations of O'Neal and Ackerman Dahlin and others who have reviewed and analyzed their own hospital material. Today I see fewer neglected chondrosarcomas and many more early ones. Most of the cases now submitted for consultation by pathologists and surgeons are presented not so much because of uncertainty as to diagnosis as because the implications of radical curative surgery are sufficiently serious for them to want a corroborative opinion.

In regard to many chondrosarcomas, it is possible from the clinical course and the roentgenographic and pathologic findings to show or deduce that they have arisen in lesions originally benign Thus, a chondrosarcoma not uncommonly develops by malignant change in a solitary benign enchondroma, especially of a long tubular

bone Again, a chondrosarcoma occasionally develops out of the cartilaginous cap of a solitary osteocartilaginous exostosis (so-called osteochondroma) Analogously a chondrosarcoma may grow from one of the numerous lesions in skeletal enchondromatosis or in multiple osteocartilaginous exostoses. A chondrosarcoma which begins its development within the interior of a bone may be denoted as a central chondrosarcoma, and one which begins in the cartilaginous cap of an osteochondroma as a peripheral chondrosarcoma. This distinction is of practical importance in that



Fig. 87 — Large peripheral chondrosarcoma of the upper femur developing in a 28-year-old male who had shown multiple exostoses since childhood. The tumor had been enlarging steadily for some 5 years and when extirpated was found to measure as much as 30 cm in its greatest dimension

amputation is mandatory for a central chondrosarcoma in a limb bone for example, whereas complete surgical extirpation of a peripheral chondrosarcoma is often possible by adequate local excision without sacrificing the affected part.

The foundation for our original discussion[10] was some 15 cases recorded in our files. Of these, 10 were central and 5 peripheral chondrosarcomas. Collaterally a background for this study was obtained by reviewing the cytology of the benign growths from which chondrosarcoma so often evolves. Drawing on our files, we

studied 27 cases of solitary benign enchondroma and 50 cases of solitary osteochondroma or osteocartilaginous exostosis. I have observed *an appreciable number* of additional cases of chondrosarcoma of various types since this original survey was made. This additional experience tends to substantiate the validity of the views expressed in this discussion and will not be related in detail. The illustrations, however have been selected from the material observed within the past 5 to 10 years, and the accompanying legends serve in a sense as highly condensed case reports.

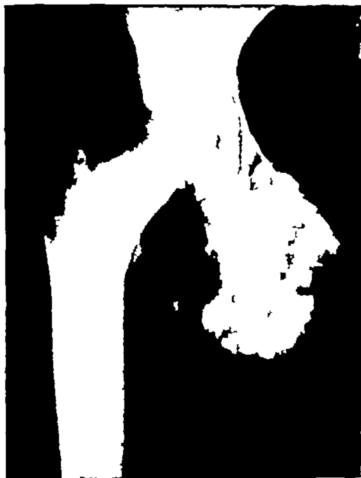


Fig 88.—Early chondrosarcoma arising in the right ischium of a 26-year-old woman. The tumor had been gradually enlarging for about 1 year and the patient sought treatment mainly because it interfered with sitting. Such tumors, if they are not extirpated while still operable, tend to enlarge steadily over a period of years and may eventually attain huge size.

Clinical Aspects

Age and Sex Incidence, and Localization.—Most of the patients with chondrosarcoma have reached adult life. In occasional instances they are still in their teens, but in the great majority they are between 30 and 60 years of age. The disorder appears to be somewhat more frequent in males. These generalizations, drawn from our own cases, seem to be in line with what one can gather from the literature. In

evaluating the latter however one must make due allowances for misclassification of cases. Many cases reported under the heading of chondroma turn out, on closer study of the report, to represent what is paradoxically labeled "recurrent chondroma" or "benign metastasizing chondroma" that is, actually chondrosarcoma. These considerations *make it difficult also to estimate from large numbers of cases, the true* incidence and localization of chondrosarcoma. It appears, however, that the long tubular bones, the innominate bones, and the ribs are the most common sites. Occurrence in hand and foot bones is observed occasionally I have also seen material from a chondrosarcoma arising in the sphenoid bone at the base of the skull as well as from several arising in nasal bones, where they present a very formidable problem in treatment. Mention may also be made in passing of invasive chondrosarcomas arising in the tracheal and bronchial cartilage, respectively but these are comparatively rare.

Clinical Findings.—In most of our cases the patients had already had a long but not dramatic history at the time of admission. This was true irrespective of the bone affected and of the central or peripheral origin of the chondrosarcoma. On the whole, the history tended to be longer in the cases of peripheral chondrosarcoma. Very short histories, associated with a rapidly fatal clinical course, are clearly exceptional (though a few have been recorded) and we ourselves have observed no cases of this kind. Thus, in a case of peripheral chondrosarcoma which evolved from a costal osteochondroma, the patient stated that for 12 years she had been aware of a painless mass which slowly grew to the size of an egg In a case in which the chondrosarcoma (a huge one) developed from an osteochondroma of a tibia, the patient stated that for 24 years he had been conscious of a slowly enlarging but not disabling tumor mass in the upper part of the leg In our case of peripheral chondrosarcoma of an innominate bone there was an 8 year history of a slowly progressive tumorous enlargement associated with scarcely any clinical difficulty Even in the case of multiple exostoses in which the chondrosarcoma developed on a rib, 2 years elapsed before the lesion had reached the size of a grapefruit and the need for treatment became urgent.

While, as noted, the histories in the cases of central chondrosarcoma tend to be somewhat shorter yet it is not unusual in such cases either for the history to date back 4 or 5 years. For instance, in one of the cases of central chondrosarcoma of a femur the patient stated that he had had dull aching local pains at intervals for 5 years, with exacerbations from time to time. It was not until he accidentally palpated a mass along the lateral aspect of this femur that he sought medical care. On the other hand, in another case in which the chondrosarcoma was in a femur the complaint was of only 6 months' standing This patient gave a history of pain and functional disability in the region of the knee worse at times, but never bad enough to confine him to bed In one of the cases of central chondrosarcoma of an innominate bone, there was a 5 year history of moderate and intermittent pain and disability in the region of the hip joint, associated with pains shooting down the entire leg

Physical examination in most instances revealed the enlargement, slight to considerable, of the area affected. The enlarged part was firm or bone-hard and usually not very tender and the overlying skin was never red or warm. When the

area involved was near a joint, the latter was likely to be found somewhat swollen and its motion somewhat restricted.

Significance of Trauma.—We analyzed our cases with reference to the possible relation of trauma to the development of the tumor. It is significant that in about half of the cases in which the data were adequate the patients stated definitely that they knew of no antecedent trauma which could have any bearing upon the lesion. Two patients in whom the chondrosarcoma developed in an osteochondroma stated that 24 and 8 years before, respectively, trauma led to discovery of a local tumescence which must have been the osteochondroma. Whether this long-antecedent trauma instigated growth and transformation of the osteochondroma into a chondrosarcoma cannot be definitely known. Our cases include one osteochondroma undergoing slow transformation into a chondrosarcoma clearly without the agency of trauma. In fact there was only 1 case among our 15 in which it was reasonable to suppose that trauma might have been a factor. This was the case of a man suffering *from multiple exostoses who received a blow to one side of the chest and who,* 6 months later, showed a definite and enlarging malignant tumor of a rib in the general region of the trauma. It should be borne in mind in this connection, however, that the natural tendency toward malignant transformation of an osteochondroma is stronger in cases of multiple than in cases of solitary osteocartilaginous exostoses. Altogether then, even in occasional cases in which there seems to be a significant factor of trauma, it cannot be accepted without some reservation.

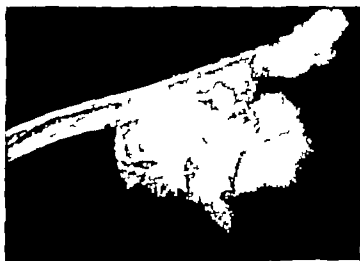


Fig. 89.—Roentgenogram of a surgically extirpated peripheral chondrosarcoma protruding from the inner aspect of a rib. Only the older central portion of the tumor is heavily calcified. This neoplasm developed insidiously and was discovered by chance in a chest film taken because the patient had developed pneumothorax following an injury. The pleura was not yet invaded by tumor and the prospect for cure in this instance is good.

Roentgenographic Findings

The roentgenographic findings may go far toward confirming the suspicion, perhaps already aroused by the history and physical findings, that one is dealing with a chondrosarcoma. Certainly a long bone presenting an irregularly mottled

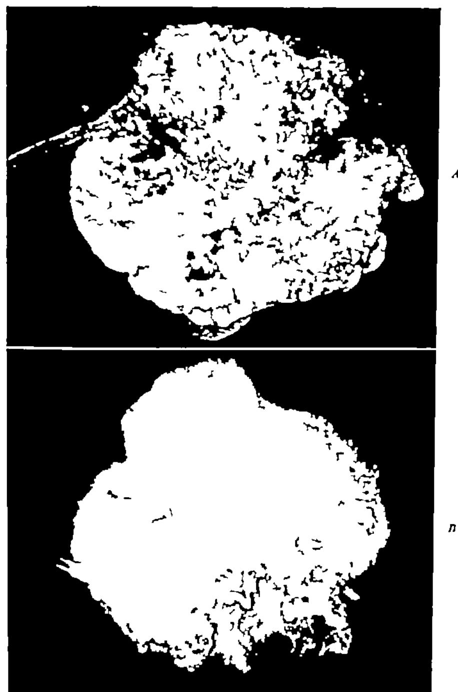


Fig. 90.—*A* Photograph (reduced to ½ natural size) of another surgically extirpated chondrosarcoma of a rib which had been slowly enlarging in the chest wall for several years. In so far advanced a chondrosarcoma it is no longer possible to trace its evolution. (Compare with tumor illustrated in Fig. 89.) *B* Roentgenogram of the chondrosarcoma illustrated in *A* emphasizing the presence of foci of heavy calcification and ossification throughout the neoplasm. At the follow-up 4 years after resection, this patient was well and apparently free of tumor

and calcified shadow in its interior and a fuzzy area of localized destruction of the cortex should make one suspect tumor of this type. This suspicion is all the more justified if where the cortex is undergoing destruction, it is somewhat thickened in part or throughout and is overlaid by tissue casting an abnormal shadow

In the absence of mottling and calcification as a clue to the cartilaginous nature of a central bone lesion, it may not be clear at all that a given malignant tumor in a long bone is a chondrosarcoma. For instance, in one of our cases the lesion initially presented itself as a somewhat trabeculated but not particularly radiolucent area involving the lower quarter of the shaft (which was slightly expanded), and part of the external condyle of a femur Were it not for the fact that the overlying cortex, especially anteriorly seemed fuzzy apparently in consequence of invasion by tissue from the medullary cavity one would have had good reason to interpret the lesion at this stage as benign and possibly as a large solitary focus of fibrous dysplasia Within a few months, however there could be no doubt that the lesion was a malignant tumor for by that time roentgenograms showed extensive destruction of the cortex and the presence of a large, extra-osseous tumor mass. However neither in this mass nor in the tumor within the bone were there mottled opacities suggesting a cartilage growth undergoing calcification and ossification. Altogether in this case, if one did arrive at a diagnosis of chondrosarcoma roentgenographically this conclusion could have been reached only by the process of elimination.

The peripheral chondrosarcomas are, on the whole, not difficult to single out. A benign osteochondroma, whether small or large, presents roentgenographically a more or less uniform texture and a well-defined peripheral outline, beyond which there are no abnormal shadows. In contrast, an osteochondroma which has undergone transformation into a chondrosarcoma presents a dense, blotchy appearance over a considerable area, usually associated with the presence of more ragged, irregular radiopaque streaks extending away from the main part of the lesion. It is the older part of the tumor, particularly that is prone to manifest heavy calcification and ossification.

Central Chondrosarcoma

The pertinent considerations here may perhaps best be presented with reference to specific case material, rather than through generalized remarks. Of the 10 cases of central chondrosarcoma, there were 5 in which development out of a less serious cartilaginous lesion could still be clearly deduced and 5 in which it could not. In the former group there was one example involving the upper end of a humerus (in a girl 19 years of age) in which the diagnosis of chondrosarcoma was based solely on the microscopic findings, the gross findings hardly giving any cue in this direction. Curettings taken for biopsy were studied originally and supplemented by a resected specimen 10 months later The resection was done because the lesion had been growing steadily since the specimen had been taken for biopsy If it had not been for the microscopic findings in certain areas of the peripheral cartilaginous cuff of the resected specimen, we might still have regarded this lesion as a benign

calcifying and ossifying enchondroma as we did on the basis of the biopsy material The patient has shown no recurrence during the subsequent 4½ years.

Our experience now includes another case in which a calcifying and ossifying enchondroma at the upper end of a humerus underwent malignant transformation. The patient was a man, 52 years of age on admission, and our original material in

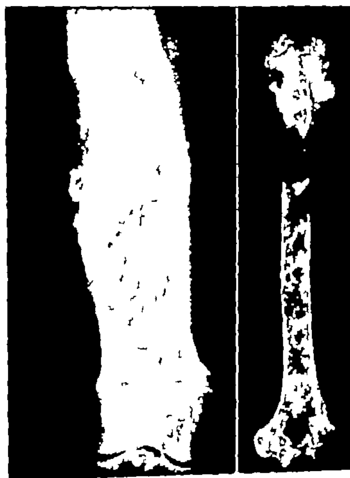


A. B.

Fig. 91—*A* Roentgenogram of a rarefied tumorlike lesion in the upper shaft and intertrochanteric region of a femur with a pathologic fracture through it, which proved to be a chondrosarcoma. From this initial x ray picture alone one could hardly venture any more definite opinion than that of a malignant neoplasm *B* Roentgenogram of the same chondrosarcoma, now heavily calcified and ossified, taken 7 years later The patient had declined the recommendation of disarticulation (which would probably have effected a cure) and he eventually developed pulmonary metastases

this case consisted merely of some curettings for biopsy On this basis, the lesion was at first regarded as a benign enchondroma, though subsequently we realized that we had "underdiagnosed" it. That this was so was borne out by the fact that within 12 months the lesion had become flagrantly malignant even clinically The upper end of the humerus was resected and showed a chondrosarcoma which had

erupted from the bone in one region. Especially where this was the case, the neoplastic tissue was no longer cartilaginous but rather of a fibrous nature and gray white in color. It appeared histologically as a rather anaplastic, collagen forming, spindle-celled sarcoma but showed no ossification. From such areas alone, it would be difficult to surmise that the tumor had developed from an enchondroma. Elsewhere, even in the *original* calcified and ossified cartilaginous *portion* of the tumor, there was evidence of activated growth of the dormant cartilage cells.



A. *B.*

Fig. 92.—*A* Roentgenogram of a central chondrosarcoma developing in the shaft of a femur and showing appreciable widening of the shaft and cortical thickening from periosteal new-bone apposition. Cortical perforation at the site of a central cartilage tumor must be regarded as an ominous sign of active growth of the neoplasm. *B* Roentgenogram of a disarticulated humerus of a man 60 years of age, showing a central chondrosarcoma which occupies the interior of the entire bone except for its distal end. The extensive calcification and ossification within the tumor indicates that it developed through malignant change in an enchondroma which had been present for many years. The recognition of malignancy was so long delayed in this instance that the tumor had already extended beyond the periosteum into the contiguous muscle tissue.

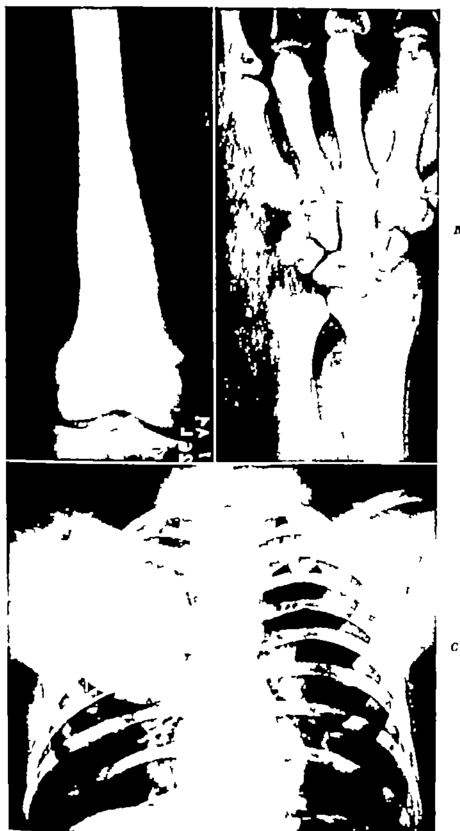


Fig 93 — *A* Roentgenogram of another central chondrosarcoma in the lower shaft of a femur (see also Fig 92 *A*) which has provoked lamellated ("onionpeel") deposition of periosteal new bone. *B* Roentgenogram of the same patient showing periosteal new bone apposition on the metacarpal and forearm bones as an expression of pulmonary hypertrophic osteoarthropathy *C* Roentgenogram showing a large solitary (slowly enlarging) metastasis in the right lung responsible for the changes illustrated in *B*

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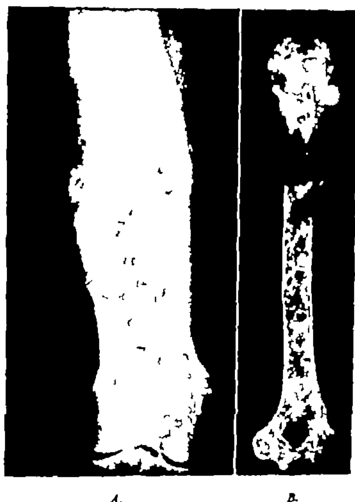
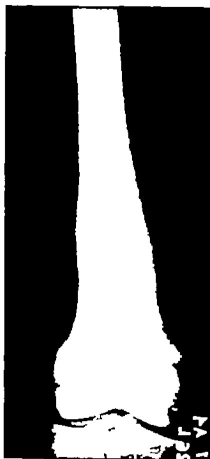


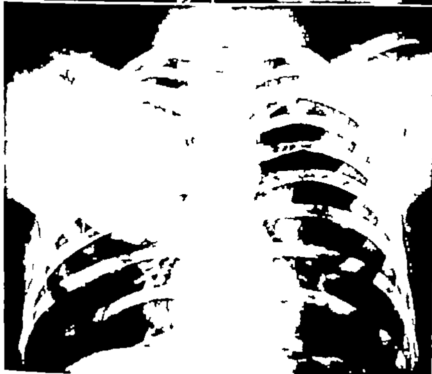
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A





B



C

Fig 93-4 Roentgenogram of another central chondrosarcoma in the lower shaft of a femur (see also Fig 92, *A*) which has provoked lamellated ("onionpeel") deposition of periosteal new bone. *B* Roentgenogram of the same patient showing periosteal new bone apposition on the metacarpal and forearm bones as an expression of pulmonary hypertrophic osteoarthropathy. *C* Roentgenogram showing a large solitary (slowly enlarging) metastasis in the right lung responsible for the changes illustrated in *B*

There were also 2 cases of femoral chondrosarcoma presenting localized *spontaneous cortical perforations* as an ominous gross feature in lesions which might otherwise have been regarded grossly as benign calcifying and ossifying central cartilage growths. In one of these the original material was an amputation specimen from a man 59 years of age. In the other the material was an entire femur obtained at autopsy from a woman of 79 years who though she had had difficulty relating to the femur for about 4 years before death, had died from bronchopneumonia and pleurisy



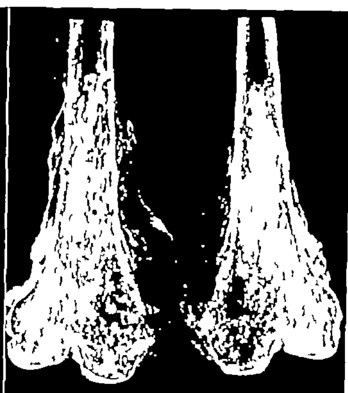


Fig 94. Fig 95

Fig 94—Central chondrosarcoma of the upper femur in an older adult, which caused partial destruction and avulsion of the lesser trochanter The presence of light calcific stippling of the central portion of the tumor affords the only cue to its recognition.

Fig. 95—Photograph (reduced) of the two halves of a lower femur amputated for chondrosarcoma in the medial condyle. Though still comparatively small the tumor had already penetrated the cortex The subperiosteal hematoma resulted from biopsy performed several days previously

In the first of these cases, the amputation had been done at the junction of the middle and upper third of the thigh, well above the level of perforation. On cutting through the femur *the surgeon unexpectedly found the marrow cavity* of the stump filled with cartilage, and, on curetting upward for several inches, also found cartilage extending above the amputation level. However since permission had been given for amputation and not for *disarticulation, nothing* further was done at that time. Within 3 months after the amputation, a revision of the stump

was done because of local recurrence and 7 months later a disarticulation was performed because there were now large masses of tumor around the remaining portion of the femur When the latter was dissected free it was found to be largely enveloped by semifluctuant tumor masses of various sizes, some of which were covered merely by periosteum while others also had muscle adherent to them. Coronal section of the specimen revealed that except at the end of the stump the medullary cavity was filled with soft, whitish and obviously cellular neoplastic tissue, extending up into the spongiosa of the metaphysis and part of the neck. Furthermore, one could see that the cortex of the shaft was permeated everywhere by tumor and that there were large pockets, bordered by modified and eroded cortex and distended periosteum and filled with soft, semifluid, or gelatinous neoplastic cartilage. From the gross appearance there could not be the slightest doubt that one was dealing with a chondrosarcoma. Within 2 years after disarticulation the patient showed another recurrence, with bulky tumor masses in the groin and also in the pelvis. There is good reason to believe that had disarticulation been done in the first instance, a cure might have been obtained in this case.

There were several cases in which the chondrosarcoma was engrafted upon lesions of Ollier's disease (skeletal enchondromatosis) In one—that of a woman 56 years of age—the left lower limb had been bumpy stubby and shortened from birth and its bones (especially the femur and tibia) were filled with cartilage plugs and nodules of widely varying size Some time before this limb was disarticulated a perforation had occurred though the cortex of the lower end of the femur medially and a large cartilaginous tumor mass of gray gelatinous tissue, continuous with the interior of the bone had developed in the soft parts of the lower half of the thigh particularly in front It was in this area that the chondromatous tissue had undergone transformation into a chondrosarcoma while, in contrast, the cartilage filling the upper half of the femur and all of the tibia showed nothing that was grossly suggestive of malignant change. Another case was that of a boy 19 years of age, whose enchondromatosis seemed to be limited to the bones of the right hand and forearm. In this case, the distal end of the ulna was found distorted by a protuberance measuring approximately 6 by 5 by 5 cm and the affected area was resected. Both longitudinal and transverse sectioning of the specimen showed that the distortion had been created by a mass of cartilage which was continuous with cartilage in the interior of the ulna, the cortex being defective over most of the region where the mass was situated. (Fig 97)

We turn now to the 5 cases of central chondrosarcoma in which, at the time of initial examination, the pathologic material yielded no evidence that the sarcoma had evolved out of a less serious central cartilaginous lesion. In these cases, the cartilage growth may have been malignant from its inception. In one instance that of a man of 39 years, an amputation specimen presenting a lesion in the lower end of a femur showed a flask-shaped distention of the affected region, 10 cm. wide, 12 cm. deep and 15 cm long The amputation level definitely cleared the tumor as far as the interior of the bone was concerned, but apparently did not clear it in relation to the soft parts and periosteum. Within 6 months after the operation, the

A

B

Fig 96.—*A* Roentgenogram of a chondrosarcoma which developed several years after x ray irradiation of the upper end of a humerus (employed to supplement curettement in the treatment of a benign chondroblastoma) *B* Photograph of a large celloidin mount demonstrating heavy calcification in the head of the humerus and widespread extension of tumor through the eroded cortex into the surrounding soft parts. The cytology of the neoplasm was that of a richly cellular rapidly growing chondrosarcoma. (Courtesy of Dr C. Howard Hatcher Chicago)



A B.

Fig 97.—*A* Photograph (reduced) of a chondrosarcoma developing in the resected distal end of an ulna of a young man 19 years of age with skeletal enchondromatosis limited to the bones of the right hand and forearm (Ollier's disease) The protruding tumor mass measured 6 by 5 by 5 cm. and was continuous with tumor cartilage in the interior of the ulna *B* Roentgenogram of the specimen illustrated in *A* The radiopaque central area reflects ossification of neoplastic cartilage.

femoral stump showed extensive rarefaction and cortical destruction, extending upward for about 10 cm., and there were also evidences of recurrence of the tumor in the soft parts about the stump Disarticulation was done On dissecting the muscles and soft tissues about the femur whitish, glistening tumor was found to be extending into the muscles and fat. A sagittal section of the stump showed neoplastic tissue extending 7 cm. up the medullary cavity and directly continuous, through defects in the cortex, with that in the surrounding muscles and fat. About 4 cm. above the main tumor mass another nodule of tumor 3 cm. in its longest diameter was found in the marrow cavity of the stump the intervening part of the cavity apparently being uninvolved



Fig. 98.—Roentgenogram in a case of skeletal enchondromatosis involving both hands (Ollier's disease) Biopsy showed early malignant change in the metacarpal bone of the right thumb (shown on the left)

We saw one case of chondrosarcoma develop apparently *de novo* in a short tubular bone specifically the basal phalanx of a finger (a rare location) The lesion was as large as a child's fist and the skin was movable over it. The tumor had destroyed most of the phalanx, sparing only the basal part. Indeed even this part showed ingrowth of a few neoplastic nodules. The tumor tissue was typically lobulated had zones of cystic softening and hemorrhage and was sharply delimited.

A somewhat different gross picture was presented by another chondrosarcoma in the lower end of a femur of a man 29 years old. Though the spongiosa in the affected area was filled with tumor the general contour of the bone itself in that area was not much modified. However, the whole lower third of the thigh was

tremendously enlarged, since the tumor had erupted through the cortex and had *grown exuberantly in the soft tissues* about the *lower* end of the femur. The site of eruption of the tumor into the surrounding soft tissues was the thin cortex just above the condyles. This gross picture (early penetration of the cortex of the affected area and luxuriant growth of the tumor in the overlying soft tissues, *without* much distention of the affected bony part) is nearly always seen in chondrosarcomas starting within a flat bone. Our records include 2 such cases, in both



Fig. 99.—Another instance of skeletal enchondromatosis affecting a lower limb (Ollier's disease) with chondrosarcomatous change in the femur.

of which the lesion originated in an innominate bone. In one of these cases, that of a man 31 years of age the tumor, starting in the left pubic bone, presented on the outside of the pelvis as a large, *lobulated*, cystic cartilage *mass extending along* the inner side of the thigh to the perineum. On the inside of the pelvis the cartilaginous mass produced a tumor which, by rectal palpation, could be found extending to the prostate. The gross material from this case consisted of numerous small irregular fragments of cartilage, most of which were firm and of a homogeneous, glassy blue-white appearance, though a few were *softer and more yellowish,*

apparently in consequence of degenerative changes. None of the cartilage showed areas of calcareous impregnation and ossification such as one would find if he were dealing with a peripheral chondrosarcoma developing from the cartilaginous cap of an osteochondroma.

In the other case, that of a man 40 years of age, the tumor seemed to have arisen in the left acetabulum, had broken into the hip joint, involved the head of the femur the ischium and pubic bone, and also formed an elastic tumor mass which spread in the pelvis toward the prostate and overlay its left lobe. Complete removal of the tumor was obviously impossible but many bits of hyaline and myxomatous cartilage were removed for examination The patient died about 5 months later at another hospital and, at autopsy a large local tumor mass was found, as well as tumor nodules along the aorta and in the right adrenal pleura, lungs, and heart.

In general chondrosarcomas of the pelvic region may attain truly fantastic size. This is favored by the difficulties of their radical treatment in this region, the high resistance of chondrosarcomas to irradiation therapy and the likelihood of delay in the appearance of distant or strategic extensions or metastases. Indeed an innominate bone which is the site of such a chondrosarcoma not infrequently comes to be embedded, over a considerable area, in a mass of neoplastic tissue 12 inches or more in diameter In addition to breaking into the hip joint and involving the upper end of the femur it may even come to involve heavily the sacrum and lumbar vertebrae.

Peripheral Chondrosarcoma

As noted, the designation of peripheral chondrosarcoma" applies to a chondrosarcoma which starts its development in the periphery (as contrasted with the interior) of a bone, and specifically in the actively growing cartilaginous cap of an osteochondroma. Of the 5 pertinent cases on which we have anatomic material and clinical data, 4 apparently were instances of solitary osteochondroma showing transformation into chondrosarcoma, while the other was an instance of multiple osteochondroma (multiple hereditary exostosis) in which one of the outgrowths had undergone malignant change. To judge from our experience, a solitary osteochondroma seems to undergo malignant change only occasionally when one considers the frequency of solitary osteochondroma among the tumorous bone disorders. The incidence of malignant transformation of one or more of the osteochondromatous outgrowths in cases of multiple exostosis seems to be higher on a case-to-case basis. This impression likewise appears to be borne out by the literature, which reveals a considerable number of such instances.

In one of our cases (that of a 44-year-old woman) the peripheral chondrosarcoma developed out of a solitary osteochondroma of the left fourth rib in which a slowly enlarging tumor mass had been known to be present for 12 years. In the extirpated piece of rib the sternal end was found encased, particularly anteriorly in a mass of lobulated tissue. This tumor mass measured 4 by 3.5 by 2.5 cm. and was covered by a fibrous capsule. It felt firm and elastic in some places and osseous in others. When the patient was seen 3 years later there was

a recurrence at the site of the original operative intervention, the tumor mass at this time being about three times the size of the original lesion. A wide resection was done, and the neoplastic tissue of the recurrent growth was found composed of large facets of cartilage still showing some evidences of calcification and ossification, especially centrally On microscopic examination, it also showed progression of its malignancy cytologically beyond what was apparent in the original specimen. Five years after resection of the recurrent lesion, Mayer reported that there had been no further recurrence in this case.

In another case of costal chondrosarcoma developing in association with multiple exostoses, it was the left sixth rib that was affected, presenting an almost grapefruit-sized tumor in the midaxillary line. Exploration showed that the mass overhung and separated the adjacent fifth and seventh ribs. It was also found that anteriorly a few small chondromatous nodules had penetrated the capsule and were separate from the main mass, and that posteriorly the tumor had penetrated the pleura. The mass was resected (though not in one piece) and its gross appearance was again found typical of peripheral chondrosarcoma. Specifically the interior of the tumor showed a rather heavy sprinkling of bone and foci of calcification among islands of cartilage. Externally there was an irregular zone of cartilage several centimeters thick in some places and clearly delimited here and there from the interior of the tumor by a line of endochondral ossification. Within 4 months this patient showed a local recurrence, and a wider local resection of the chest wall was done at another institution. At this operation the recurrent tumorous cartilage was found to be practically devoid of the calcification or ossification so typical of peripheral chondrosarcoma, at least in the original specimen. Several months later there was again evidence of recurrence. The patient died almost 2 years after the original operative intervention, and 4 years after he had first noted the presence of the tumor At autopsy considerable gelatinous cartilage was found beneath the soft tissues of the chest wall. Adherent to the pleura, there was a mass of the same type of tissue, practically filling the entire plural cavity on the affected side and encasing and collapsing the lung There were no visceral metastases. The autopsy confirmed the presence of numerous cartilaginous exostoses on various bones, thus establishing the diagnosis of multiple exostoses already made earlier on a roentgenographic basis.

Another pertinent case (that of a man 46 years of age) in which the peripheral chondrosarcoma developed from an osteochondroma on a tibia is interesting in that the patient had been aware for 24 years of a hard lump at the upper and outer margin of this bone. During this time the lesion had grown only very slowly but, about 2 months before the patient's admission to the hospital, it began a spurt of growth, apparently after local trauma, and became increasingly painful. On admission a large, hard, bony mass, 6 inches in diameter was palpable on the anterolateral margin of the tibia 1 inch below the tubercle and on the anteromedial border about 3 inches below the joint, a smaller mass was palpable. At operation it was found that the tumor which had arisen from the tibia, lay both anteriorly and posteriorly to the interosseous membrane. The neoplastic tissue was removed piecemeal but not all of it could be removed. Nevertheless, a quart of tumor

material was obtained and submitted for pathologic examination. Grossly by piecing the bits together one could see that centrally in the tumor mass there was much calcification and ossification and that peripherally there was an undulating wide cap of cartilage containing only streaks of calcification. About 5 weeks later the limb was amputated above the knee joint and during the ensuing 2 years the patient showed no evidence of recurrence.

The findings in our other 2 cases of peripheral chondrosarcoma are essentially in line with those already indicated. One was a case of tumor of the left innominate bone occurring in a woman 30 years of age who dated her difficulties from a fall 8 years before admission to the hospital. On admission, a huge tumor was palpable on the iliac portion of this bone. The other case was that of a woman, 59 years of age, in whom the lesion was in the left scapula. Although the scapula had been converted into a lobulated mass of the size and shape of a small football, it was mainly because of neurologic symptoms referable to pressure on the brachial plexus that the patient was admitted to the hospital.

Extension and Metastasis

If untreated, chondrosarcomas (central or peripheral) are likely to remain only locally invasive for years. After an initial surgical intervention, a local recurrence is certainly to be expected if the tumor has not been widely excised. Local recurrence of the lesion in even bulkier form is almost the rule at subsequent interventions under these circumstances. However even then there may still be no definite spread of the growth for a long time, and death may take place from other causes. When a chondrosarcoma finally does spread, it tends to break into the regional venous channels, and by intravascular growth and extension, without necessarily adhering very much to the vessel walls, may reach the heart and lungs. Though it is ordinarily years before this occurs, in an occasional case the disorder runs its course so rapidly that the patient is dead within some months after the original tumor in the bone is first noted. The presence of severe respiratory and cardiac difficulties for a time before death in a patient with chondrosarcoma may well be a clinical indication that cordlike intravascular growth and extension of the tumor to the heart and lungs has taken place.

A remarkable example of such neoplastic extension is the case, described by Ernst, of a chondrosarcoma involving the lower part of the vertebral column. In this case there were tumor plugs in both the renal and the suprarenal veins, the left internal spermatic vein, the azygos vein, the inferior vena cava, the right auricle, and the branches of the right and left pulmonary arteries and still the pulmonary parenchyma was free from metastases. Kósa described a femoral chondrosarcoma with neoplastic extension to the ipselateral femoral and iliac veins, the inferior vena cava, the right heart, and both branches of the pulmonary artery even to the capillaries again without the occurrence of any parenchymal metastases, even in the lungs.

In other cases while extending into the large venous channels, the tumor also gives rise to parenchymal metastases, at least in the lungs. In the case described by Weber there were metastases not only in the lungs but also in the liver (around

tumor plugged branches of the portal vein) but in the case reported by Warren the metastases were limited to the lungs. Actually metastases elsewhere than in the lungs are uncommon in connection with chondrosarcomas. The possibility of lymphatic spread also exists, and extension of the tumor to lymph nodes, especially regional, has occasionally been reported. However it is to be recognized that small secondary nodules of tumor not far from the primary mass might easily be wrongly interpreted as representing lymph nodes which have undergone complete replacement by tumor

Significant Cytologic Findings

In evaluating the cytology of a chondrosarcoma, as in evaluating that of an enchondroma or an osteochondroma, attention should likewise be concentrated solely upon areas which are viable and not heavily calcified or ossified The reason is that in areas which are undergoing necrosis, heavy calcification, or ossification, the cartilage cells (and particularly their nuclei) are likely to be swollen because of these changes that is, for reasons irrelevant to the benignancy or malignancy of the lesion. A chondrosarcoma may violate the histologic criteria of benignancy to such an extent that even without knowing anything about the gross appearance of the lesion the examiner becomes aware of its malignancy at a glance. On the other hand, a chondrosarcoma may deviate from the criteria rather subtly and require for its proper diagnosis, detailed scrutiny under high magnification, of many microscopic fields, and more material than is ordinarily obtained for biopsy by a punch. When this is the case, the lesion is often underdiagnosed" histologically at least at first as a benign enchondroma or osteochondroma, its chondrosarcomatous nature not being appreciated until a recurrence appears and perhaps reappears. We ourselves had originally "underdiagnosed" a number of our cases, as was impressed upon us by subsequent sad experience with them.

The case in which the lesion was in the upper end of a humerus represented an instance of very early and subtle deviation in the direction of malignancy Histologically on the basis of the original biopsy one could not have entertained, in this case, any other diagnosis than that of a benign enchondroma. Ten months later however the cartilage of the resected specimen showed, especially in parts of the peripheral zone, an unequivocal change in the direction of malignancy Specifically as compared with those of the specimen taken for biopsy the cartilage cells in these areas, though small on the whole, had plump nuclei. Furthermore, some fields, here and there, showed a significant sprinkling of cells with two or even four nuclei, and also a number of large cells, each of which had a large nucleus.

The case of the rather small peripheral chondrosarcoma developing out of an osteochondroma of a rib again shows the necessity of searching for and paying close attention to, cytologic abnormalities which may not be obvious at first sight. In the wide cartilaginous cap of this lesion also the cells were, on the whole, somewhat plump and in some areas more than a sprinkling of them were binuclear while here and there some definitely large ones with single large nuclei were also encountered. In the recurrence studied 3 years later the lesion showed unmistakable

histologic evidences of progression in malignancy Almost everywhere, but more definitely in some fields than in others the lesion was very cellular and the cartilage cell nuclei were plump, on the whole. Many more binuclear cells and many more large cartilage cells with single large nuclei were seen This was the picture not only at the periphery of the recurrent lesion but to a very great extent in the cartilage lying among calcified cartilage and osseous material in the interior of the lesion (Fig 100)

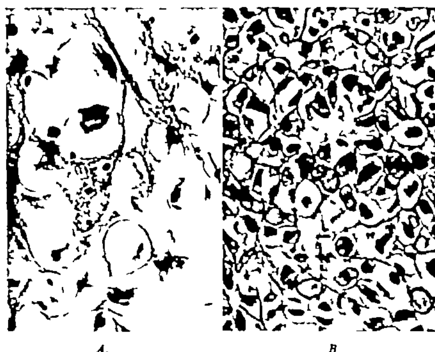


Fig 100.—A Photomicrograph of a field in the actively growing cartilage cap of a peripheral chondrosarcoma of a rib The presence of even occasional fields such as this suffices to establish a diagnosis of chondrosarcoma This tumor was not excised sufficiently widely and recurred locally 3 years later (×?50) B The cytologic picture of the recurrent tumor in this case showing obvious evidences of frank malignancy Fields such as this no longer had to be searched for and were present throughout the tumor even in its calcified and ossified areas. (×250)

Eventually in a fully developed chondrosarcoma central or peripheral, the neoplastic tissue becomes richly cellular In addition, it shows striking irregularity in the size of the cells and their nuclei, the presence of numerous plump cells with multiple nuclei, pronounced hyperchromatism of the nuclei, and the presence of many uninuclear giant cells. From lesion to lesion there are variations in detail However if material taken at different times is examined, the general cytologic picture of that particular lesion tends to remain more or less consistent, though one can usually trace cytologically the progression of malignancy from one specimen to another In the terminal phase of its evolution a chondrosarcoma may become dedifferentiated in part or substantially throughout, and revert to a more primitive spindle-cell type without any discernible chondroid matrix. In fact, it may be difficult

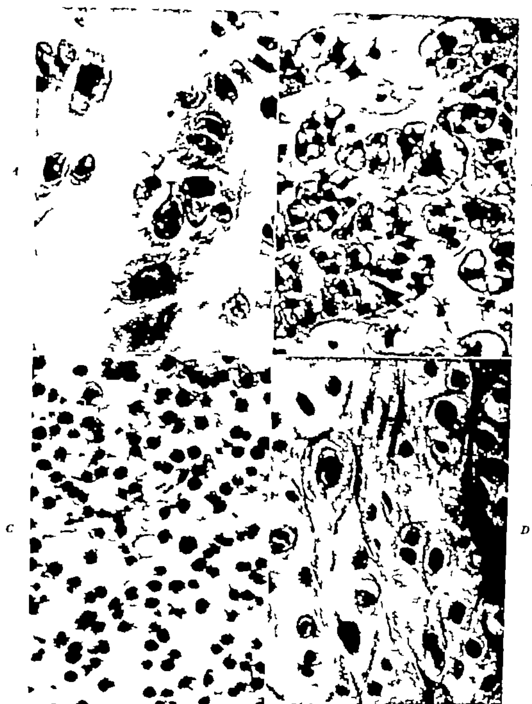


Fig. 101 — A and B Fields from a central chondrosarcoma in the shaft of a femur (comparable to the tumor in the humerus illustrated in Fig. 92 B) which recurred repeatedly following incomplete removal and eventually extended into the pelvis. (×230) C and D Representative fields from two other frank chondrosarcomas of the femur for which amputation was performed. Even in its fully evolved state a chondrosarcoma often fails to show mitotic figures or anaplasia although, to be sure, it becomes richly cellular, presents many cells with two or more nuclei, and on occasion may exhibit fibroblastic dedifferentiation as a terminal manifestation.

to identify such a tumor as chondrosarcoma without recourse to previous specimens.

In the histologic diagnosis of chondrosarcoma, not too much importance should be attached to the scarcity or even absence of mitotic division figures. If one concentrates attention upon these, one may miss the diagnosis, since cell division in chondrosarcomas tends to be amitotic. This does not mean that advanced chondrosarcomas may not show more than a sprinkling of mitotic division figures, but when they do, the histologic diagnosis is already obvious for other reasons.

Partial or extensive alteration in the character of the cartilage matrix—that is, change from hyaline to myxoid or mucoid—is not a particularly significant element in the composition of chondrosarcoma. It is true that, especially in the more bulky growths, larger or smaller areas of semisoft or gelatinous cartilage are likely to be found. However, these represent merely a nonspecific, secondary degenerative change whose incidental character is usually attested by the presence elsewhere of areas of hyaline cartilage. Chondrosarcomas which show extensive myxomatous degeneration are often designated as myxochondrosarcomas. It seems to us, however, that the prefix *myxo-* might well be dropped even in these cases, since there appears to be no special reason for this emphasis on an aspect of the pathologic picture which is not distinctive and which has nothing to do with interpretation of the lesion with respect to malignancy.

The presence in a cartilaginous growth of some or even considerable calcification and ossification is not inconsistent with its being a chondrosarcoma. In a central chondrosarcoma, such areas may be regarded merely as evidence that the growth had been benign in the past and that it had matured and regressed to some extent at some time before undergoing revivescence and malignant transformation. In a peripheral chondrosarcoma, some calcification and ossification of the matrix, at least in the early phases of the growth, are to be expected. They should not, though they often do, lead one to designate the lesion as a chondro-osteosarcoma or an osteochondrosarcoma and thus to imply that it represents a form of osteogenic sarcoma. Even if an osteochondroma is tending toward malignancy, it is in the nature of its proliferating cartilage cap to undergo calcification and ossification in the course of its development.

Treatment

The only form of therapy which offers any prospect of cure in cases of chondrosarcoma is surgery. Irradiation therapy is hardly of any value, since this type of tumor is highly resistant to such treatment, tending to continue or resume its growth in spite of it. Irradiation may serve at most as a palliative agent for a chondrosarcoma in a site inaccessible to surgical intervention, and should not be used with any greater expectation.

Surgical treatment of chondrosarcoma should be definitely on the radical side, and the wider the margin of supposedly normal tissue the better. A radical procedure offers the best promise of success when it is undertaken at the initial intervention, and this cannot be emphasized too strongly. For instance, if the tumor seems clinically and roentgenographically to be confined to the lower half of a

femur but the surgeon on amputating finds cartilage in the marrow cavity of the bone at a level which he had thought would clear the lesion it will be advisable to disarticulate at the hip joint immediately also removing as much of the capsule of the hip joint and overlying muscle and other soft tissues as is feasible. Otherwise, a recurrence in the amputation stump is almost inevitable and when this has taken place disarticulation at the hip joint is very likely to be too late to save the patient. As a part of the general principle of giving the lesion a wide margin in any site the policy of keeping one joint ahead of the growth is a valuable one. Indeed, in connection with chondrosarcoma of one of the bones of the foot, for instance, it is advisable to amputate above the ankle joint rather than to attempt excision. On the same basis, if the lesion is in a rib certainly several inches of the rib on each side beyond the region of apparent involvement, and at least corresponding sections of the rib above and below the affected one, should be sacrificed. In the treatment of chondrosarcoma of the innominate bones, it is often necessary to resort to hindquarter *amputation if one is to strive for cure. The published surveys indicate that all but* a few of the cures obtained by this radical procedure are accounted for by chondrosarcomas and that the cure rate for chondrosarcoma specifically is in the neighborhood of 50 per cent. The hopeful aspect of radical surgery (and specifically of the prevention of recurrence by keeping well ahead of the growth) in cases of chondrosarcoma lies in the fact that as a rule the tumor has not yet metastasized at the time of the initial surgical intervention.

Summary

Chondrosarcoma should be regarded as a neoplasm distinct from osteogenic sarcoma of bone. The former develops out of full-fledged cartilage, while the latter issues from more primitive tissue, developing out of bone-forming mesenchyme. Some chondrosarcomas do show large areas in which the intercellular matrix of the tumor cartilage has become heavily calcified or ossified, and in some osteogenic sarcomas, tumor cartilage in considerable amounts may be formed in the course of osteogenesis from the primitive mesenchyme. However in a chondrosarcoma, in *contrast to an osteogenic sarcoma, one* never sees tumorous osteoid tissue and bone which is evolving out of a sarcomatous stroma directly, such as one always sees *somewhere in an osteogenic sarcoma*, no matter how much cartilage it contains.

In comparison with osteogenic sarcoma, chondrosarcoma is definitely less common, appears at a later age (on the average) runs a much slower course and especially if given radical surgical treatment at an early stage, has a much better prognosis, since the tumor has usually not yet metastasized at the time of initial surgical intervention. Even when the tumor is inadequately extirpated, it tends to recur locally one or more times before extending to the tributary veins or to the lungs. Local trauma does not seem to be an important factor in the initiation of chondrosarcoma or in the malignant transformation of the benign growths (enchondroma and osteochondroma) from which chondrosarcomas so often evolve.

A chondrosarcoma which begins its development within the interior of a bone may be denoted as a central chondrosarcoma, and one which begins in the cartilag-

mous cap of an osteochondroma as a peripheral chondrosarcoma. It is in the peripheral chondrosarcomas and those central ones which have clearly evolved from benign enchondromas that one finds, at least in the earlier stages of evolution of the lesion, heavy calcification or ossification of large parts of the intercellular matrix of the tumor cartilage. In other chondrosarcomas the relevant neoplastic tissue is likely to consist, in the main, of compacted islands of cartilage with hyaline matrix, though if the chondrosarcoma is very bulky one may also see areas in which the cartilage is softer and myxomatous, and perhaps even necrotic.

The histologic picture of any particular tumor does not have to be crudely and obviously sarcomatous to indicate chondrosarcoma. Even in the early stages of the evolution of a chondrosarcoma, one will find, at least in scattered fields, if adequate material is examined, subtle but telltale evidences of cytologic atypism of the cartilage cells which will betray the malignant character of the lesion. We hold that a cartilage tumor should no longer be regarded as benign if, when viable and not heavily calcified areas are examined, it shows, even in scattered fields (1) many cells with plump nuclei (2) more than an occasional cell with two such nuclei and especially (3) any giant cartilage cells with large single or multiple nuclei or with clumps of chromatin. We feel that, by observing these criteria, the prevalent tendency to "underdiagnosis" of chondrosarcoma in an early stage of malignancy can be overcome. In a more fully evolved chondrosarcoma these indications will be relatively easy to find if one recognizes their diagnostic importance, and in a fully developed chondrosarcoma, of course, the histologic picture may even be obviously sarcomatous.

From a clinical point of view it may be emphasized that evidence of cortical perforation and the onset of pain in a cartilage growth which has previously been dormant are likely to be ominous signs pointing to early malignant change and the necessity for biopsy and appropriate surgical therapy. If a chondrosarcoma is recognized early and is widely cleared at the first operation, the chances of obtaining a cure are fairly good and in any event, very much better than with osteogenic sarcoma.

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XV

Osteogenic Sarcoma of Bone

Osteogenic sarcoma is probably the most frequently encountered primary malignant tumor of bone, with the possible exception of multiple myeloma (many instances of which go unrecognized clinically or are mistaken for skeletal carcinomatosis) The differentiation of osteogenic sarcoma from chondrosarcoma of bone has already been considered in connection with the latter tumor (see Chapter 14) To reiterate, chondrosarcoma develops from full fledged, clearly differentiated cartilage, while osteogenic sarcoma takes origin apparently from more primitive bone forming mesenchyme Ordinarily in an osteogenic sarcoma, the proliferating connective tissue, which often is quite anaplastic, gives rise to tumor osteoid and bone directly though it may also form some tumor cartilage, which in turn tends to undergo rapid osseous transformation. It is true that in an occasional osteogenic sarcoma, bone formation may proceed prominently via an intermediate cartilage stage, and tumor cartilage may thus be a conspicuous feature of its cytology However even in such an osteogenic sarcoma, if the observer does not limit his scrutiny to a small field of the tumor and particularly to the periphery of it, he will readily perceive that in other places, the basic connective tissue is directly forming neoplastic osteoid tissue and bone With few exceptions, it should be possible to make a clear pathologic distinction between chondrosarcoma and osteogenic sarcoma and, by the same token, there seems to be little justification for retaining such equivocal hybrid designations as chondro-osteosarcoma or osteochondrosarcoma.

Clinically also, there are significant differences between chondrosarcoma and osteogenic sarcoma. Thus, osteogenic sarcoma is more frequent It occurs, on the whole at an earlier age (*with the exception of the occasional instances* complicating Paget's disease) pursues a more rapid course metastasizes to the lungs relatively early and hence is more serious, even when amputation is resorted to as soon as the condition is recognized. By comparison, chondrosarcoma, as a rule, has a distinctly more favorable prognosis provided that the neoplasm is in a surgically accessible site is not underdiagnosed through failure to recognize subtle histologic

criteria of early malignant change, and is widely cleared surgically at the li operation. The practical importance of distinguishing between chondrosarcoma osteogenic sarcoma is thus evident.

Fibrosarcoma of bone also, should be clearly distinguished from osteog sarcoma, and I am in full accord with those who depart from the classificatio the Bone Sarcoma Registry in recommending that central fibrosarcoma be rem from the category of osteogenic sarcoma and considered as an independent plasm. The nature and behavior of such neoplasms, and they are by no m rare, will be considered later (Chapter 16) Essentially they represent malig fibroblastic tumors which arise in the interior of the affected bone, and which thorough histologic sampling fail to show any indication that the tumor cells actually forming tumor osteoid and bone. Like chondrosarcoma, fibrosarcom bone in most instances also carries a better prognosis than does osteogenic sarc and can be cured by radical surgery if the tumor has not already metastasize the lungs.

In the revised classification of bone tumors of the American College Surgeons Registry (1939) one finds outlined still other subdivisions of the "os genic series, so-called, such as medullary and subperiosteal, telangiectatic, sclerosing, but I feel that retaining these is not particularly helpful and that makes the subject unnecessarily confusing By the time their presence is recogni virtually all osteogenic sarcomas are found to involve the medullary cavity to have extended through the cortex beneath the elevated periosteum or e beyond it, into the adjacent muscle tissue. Also some osteogenic sarcomas are m richly vascular than others and some display more abundant new bone forma than others, to be sure, but such distinctions are of little practical importance. state the issue bluntly a given neoplasm of bone is either an osteogenic sarc or it is not, and if it is one, its prognosis is serious, whether it is richly vasc or only moderately so whether it forms abundant tumor bone (sclerosing) relatively little (osteolytic) Incidentally it was found that about one quarte the osteogenic sarcomas in our material showed relatively little ossification, anot quarter a moderate degree of ossification, and about one half rather heavy ossif tion, obviously reflected roentgenographically

Clinical Features

Age and Sex Incidence.—The tumor appears to develop more often in ma than in females. Its greatest incidence is in the age group between 10 and years, and its next smaller peak of incidence is in older adults with Paget's dise However osteogenic sarcoma is by no means rare in patients in their 30's or 4 who show no evidence of Paget's disease.

Location.—The commonest sites of occurrence are the lower end of femur the upper end of the tibia and the upper end of the humerus, in the or indicated. Occasionally an osteogenic sarcoma may be encountered in the up end of the fibula, in the iliac bone, in the vertebral column, or in a jaw bone, a

rarely in other sites. In a long bone, it is usually the end of the shaft and part of the adjacent epiphyseal area that are involved but occasionally the tumor may develop more toward the mid-shaft region (Fig 102 *B*)

Clinical Picture.—As with most tumors of bone, pain and swelling of the affected part are the usual presenting complaints. In patients (especially children) with rapidly growing sarcomas (e.g., in the lower femur) appreciable weight loss



Fig 102.—*A* *B* and *C* Representative roentgenograms of several osteogenic sarcomas developing in the lower femur The sclerosing tumor illustrated in *B* is situated in the shaft rather than the end of the bone. The osteogenic sarcoma illustrated in *C* is noteworthy in that it shows "onionpeel" lamellation of periosteal new bone rather than the more usual perpendicular striation.

and moderately severe secondary anemia may also be observed, and under these circumstances, pathologic fracture is not uncommon. In such instances in which the tumor eventually attains a very considerable size if allowed to follow its natural course, the affected limb becomes obviously swollen and its surface veins conspicuously dilated.

The interval between the onset of symptoms and the recognition of the neoplasm may vary from just a few weeks to 6 months or more. That the tumor develops insidiously is evidenced by the fact that it may be as large and far advanced in a patient presenting a history of only a few weeks duration, as in a patient who has been aware of a growth for many months before seeking medical advice



Fig 103.—*A* and *B* Representative roentgenograms of two sclerosing osteogenic sarcomas developing in the mandible.

Blood Chemical Findings as an Aid in Diagnosis.—There are no significant changes in the serum calcium or phosphorus levels in cases of osteogenic sarcoma. However as one might expect, the serum alkaline phosphatase value (which in general reflects a tendency to new bone formation) is significantly increased up to 20 or more Bodansky units in many instances, though by no means all. In such instances, there is a trend to decline to a more nearly normal level following removal of the primary tumor by ablation, and to return to the initially high level or even beyond it when the presence of pulmonary metastases becomes evident.



Fig 104—A rapidly growing, neglected osteogenic sarcoma arising in the maxilla of a 17 year-old Indian boy The tumor was already far advanced when he sought treatment, although he had been aware of it for only 2½ months. (Courtesy of Dr M. V Sirsat, Tata Memorial Hospital, Bombay.)

Roentgenographic Appearance

The ease with which an osteogenic sarcoma may be recognized roentgenographically in any particular instance depends largely upon how clear the indications are of cortical perforation and subperiosteal extension (as an expression of malignancy) and upon how evident the tendency to new bone formation within the neoplasm happens to be (as an indication of its osteogenic character) In approximately half the cases of any sizable series of osteogenic sarcomas (the highly sclerosing tumors particularly) both of these features will be so obvious that even a relatively inexperienced observer will have no difficulty in properly interpreting them. It should be emphasized, however that if one necessarily expects to find conspicuous perpendicular striations of new bone within the subperiosteal tumor cuff—a sign upon which undue emphasis has been placed—one is likely to miss a considerable number of osteogenic sarcomas. Moreover this perpendicularly striated pattern of periosteal new bone formation is not specific for osteogenic sarcoma, and I have observed it, on occasion, in cases of metastatic carcinoma, of advanced Ewing's sarcoma, and even of tuberculosis of the shaft of a long bone, so that one must consider the picture as a whole in relation to the relevant clinical

facts before reaching a conclusion. An important corollary of this observation is that one is never justified in recommending ablation without confirmation by biopsy, however certain one may be of the accuracy of the roentgen diagnosis.

In approximately another third of the cases of osteogenic sarcoma, the features just described will be apparent, though perhaps not obvious, and the examiner may have to scrutinize the films closely to discern them. In another smaller group



Fig 103.—*A* Roentgenogram of a sclerosing osteogenic sarcoma in an unusual location, the lower end of a humerus. There is a healed fracture at the upper limit of the tumor *B* Another unusual osteogenic sarcoma developing in the lower metaphysis and shaft of a radius in a child. *C* A sclerosing osteogenic sarcoma in the upper shaft of a humerus showing a pathologic fracture

of cases these features may be scarcely evident and I have observed proved instances of osteogenic sarcoma (essentially osteolytic in nature) that defy recognition roentgenographically even on the part of a skillful observer In such instances, although one may entertain a suspicion of osteolytic osteogenic sarcoma, the diagnosis must rest essentially upon the biopsy findings.



Fig. 106—Roentgenogram of an osteogenic sarcoma breaking out of an iliac crest. Although the tumor is essentially osteolytic it displays sufficient radiopaque mottling to enable one to suspect the correct diagnosis.

Pathologic Features

By the time one has an opportunity to examine a specimen amputated for osteogenic sarcoma, one finds, as a rule, that, while the bulk of the neoplasm is present within the medullary cavity of the affected bone area, the tumor has already extended through the cortex beneath the raised periosteum, where it forms a cuff extending around part of the circumference of the bone. Further an osteogenic sarcoma that is far advanced may already have broken through this periosteal barrier and invaded the contiguous muscle tissue. From the examination of many such relevant specimens, one gains the distinct impression that osteogenic sarcoma originates within the interior of the affected bone area, though it readily penetrates the cortex to spread beneath the overlying periosteum. In the course of its extension, it may leave the affected cortical area substantially intact, apparently

because the latter is permeated by tumor too rapidly to allow for appreciable resorption or for gradual expansion, such as one observes with chondrosarcoma on occasion.

The central portion of the tumor is the most heavily ossified although the extent of ossification, as noted, varies from specimen to specimen. At one extreme, there are essentially osteolytic tumors that require roentgen examination of serial slices of the specimen for the clear demonstration of occasional, rather small, densely mottled foci of new bone formation. These osteolytic tumors are rather likely to show appreciable necrosis, cystic softening, hemorrhage, and telangiectasis, as conspicuous secondary features of their pathologic anatomy At the other extreme, as is well known, there are highly sclerosing tumors which are so hard as to be substantially eburnated. On the other hand, the peripheral (subperiosteal) cuff of tumor is likely to be comparatively cellular and soft and whitish in appearance, although it, too usually displays prominent striae, or more delicate and irregularly dispersed streaks of tumor bone within it.

The most cellular and least differentiated portion of an osteogenic sarcoma is usually represented by its advancing core within the medullary cavity This conical plug of tumor tissue, which often measures several centimeters in length, may fail to exhibit any demonstrable evidence of ossification, even on roentgen examination, a factor that must be considered in determining the optimum level of amputation. An occasional specimen may show skip extension of tumor within the medullary cavity and this possibility must also be borne in mind. In regard to extension toward the end of the affected bone, it should be noted that a tumor which develops in the metaphyseal region of a long bone, e.g., the lower end of a femur tends to involve also part of the adjacent bone end (the epiphyseal area, if fusion has not yet taken place) While this may not be evident in a single random frontal or sagittal section of the specimen it can usually be demonstrated on serial section. Where the tumor extends beneath the articular cartilage, the latter acts as an effective barrier However an osteogenic sarcoma may readily involve a neighboring joint through invasion of the capsule at the site of its attachment to the affected bone area, in which case one is likely to encounter blood-tinged synovial fluid.

The histologic pattern of osteogenic sarcomas is so variable that no two specimens are exactly alike. In any event, whatever this pattern may be in any particular instance the essential criteria for the diagnosis of osteogenic sarcoma are (1) the presence of a frankly sarcomatous stroma and (2) the direct formation of tumor osteoid and bone by this malignant connective tissue. As noted, one may observe, in addition, more or less prominent fields of malignant tumor cartilage undergoing calcification and osseous transformation, but this should not alter one's impression of osteogenic sarcoma. In any given tumor the connective tissue stroma may be composed predominantly of large, atypical spindle-shaped cells or may be distinctly anaplastic and present a polymorphous cellular pattern, replete with tumor giant cells. Irregularly dispersed within this sarcomatous stroma, one observes fields in which osteoid and osseous transformation is in active progress. This may

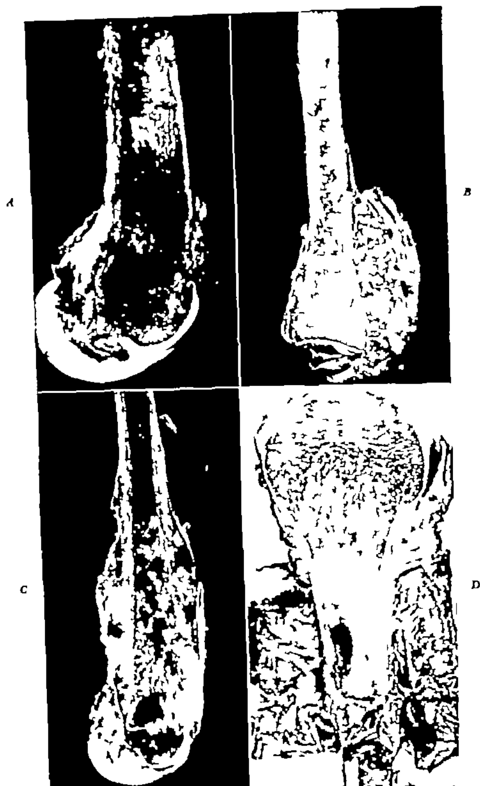


Fig 107—*A B C* and *D* A group of four amputation specimens illustrating some of the features of the gross pathologic anatomy of osteogenic sarcoma referred to in the text. The tumor shown in *B* is unusual as to location (lower end of a tibia) and presented an equivocal x-ray picture clinically The tumor shown in *D* developed so insidiously that a pathologic fracture was its first manifestation. Despite the brief clinical history there were already tumor nodules within the deltoid muscle.

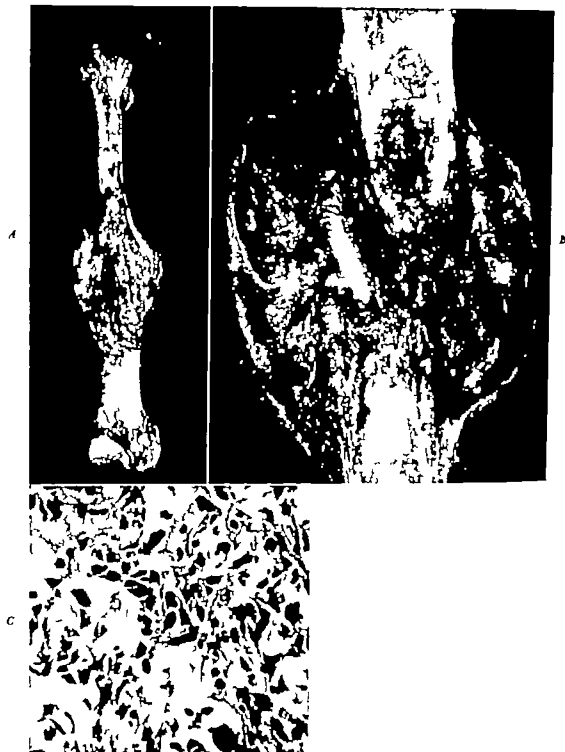


Fig 108.—*A* and *B* Photographs of a disarticulated femur showing an essentially lytic osteogenic sarcoma in its midshaft, which has destroyed the continuity of the bone and has extended beneath the raised periosteum. The patient was not aware of the neoplasm until he sustained a pathologic fracture about one month before surgery was performed. *C* A representative field of the osteogenic sarcoma illustrated above, showing the formation of osteoid matrix by the malignant tumor cells.

be preceded by collagenization of the intercellular matrix, often in the form of crisscrossing streamers, which, in turn, undergo osteoid conversion and focal calcification. The tumor cells which become enveloped in this intercellular matrix usually appear smaller more rounded, and less ominous than those of the neighboring sarcomatous stroma, which has not as yet undergone collagenization and ossification.



Fig 109—Photograph (natural size) of a resected specimen of an osteogenic sarcoma in the wing of an iliac bone. The tumor extended into attached muscle on both sides. The encapsulation of sarcomas can be very deceptive, and an attempt at clearance by so slender a margin is hardly to be recommended.

If the neoplasm is one in which relatively little tumor osteoid and bone is laid down, the original spongy bone undergoes substantial resorption and dissolution. On the other hand, if the sarcoma is one that displays extensive osteogenesis, one observes in the highly sclerotized areas within the interior of the affected bone area that the deposits of tumor osteoid and bone have been built around the original spongy bone framework as a scaffold or have freely extended between the spongy trabeculae with consequent obliteration of the marrow spaces. In such sclerosing tumors, the heavily ossified areas of tumor tissue outside of the cortex also show the intermingling of actively ossifying tumor tissue with reactive, non tumorous, periosteal new bone.

(Text continued on page 203.)

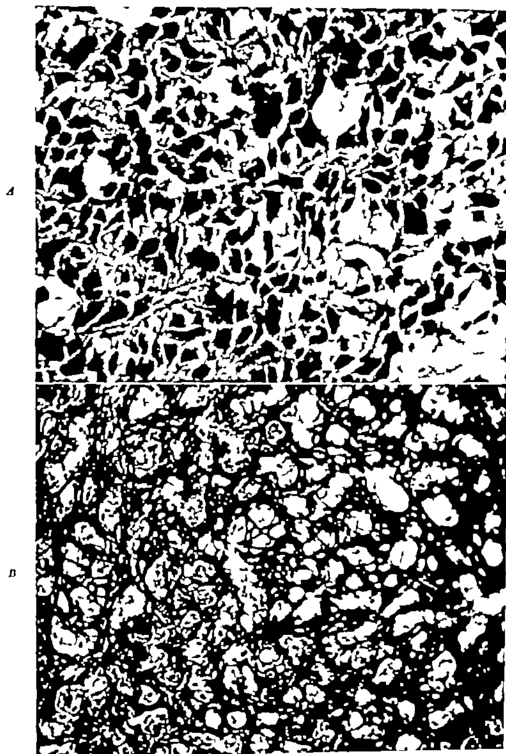


Fig 110.—*A* Photomicrograph of a field of an osteogenic sarcoma showing the formation of intercellular osteoid matrix by a frankly sarcomatous cellular stroma. (×400.) *B* A representative field of a sclerosing osteogenic sarcoma showing interlacing streamers of collagen which have undergone calcification and osteoid conversion. (×100.)



Fig 111.—*A* Photomicrograph showing formation of tumor bone within a sclerosing osteogenic sarcoma. *B* A field from another osteogenic sarcoma showing the formation of neoplastic cartilage. This may be a prominent feature in some pertinent tumors and inconspicuous in others. (×110)

A

B

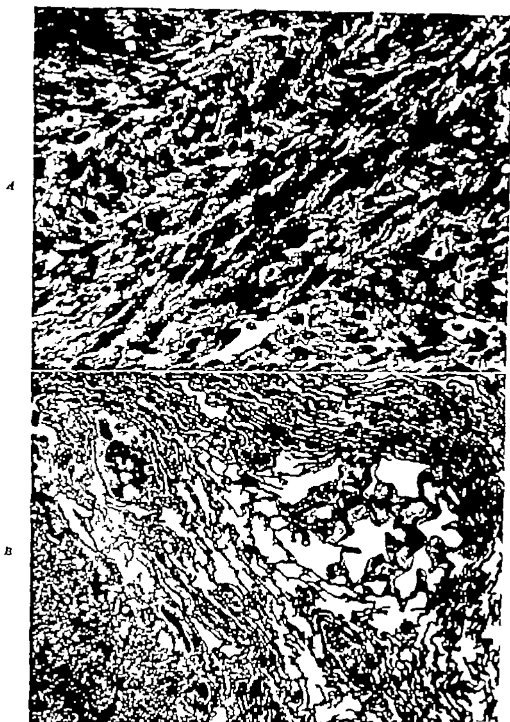


Fig 112.—*A* A field from the periphery of an osteogenic sarcoma which, if viewed in a limited biopsy specimen without due consideration of the character of the neoplasm as a whole, might lead to a false impression of fibrosarcoma. *B* Photomicrograph showing that in the pulmonary metastases of an osteogenic sarcoma one also observes neoplastic bone formation.

Metastasis in osteogenic sarcoma occurs almost exclusively by hematogenous spread and extension to regional lymph nodes although it has been noted, appears to be of infrequent occurrence Pulmonary metastases are consistently present in cases which come to autopsy Judging by serial roentgenograms, these may start out as discrete multiple foci (usually also ossified) which, as they enlarge, tend to coalesce, so that ultimately one is likely to find a bulky solid tumor mass within the mediastinum and/or one or another of the lungs. On occasion one may observe late metastases in one or more of the other bones, but visceral metastases aside from those in the lungs are unusual. In this terminal stage also cachexia, decubitus ulcers, flexion contractures, and secondary anemia reflected anatomically in hemosiderosis of the reticulum-bearing organs are common findings.

Sarcoma Complicating Paget's Disease

It is a well-known observation that sarcoma of bone develops with significant frequency in patients with Paget's disease. This complication is usually observed in patients with fairly extensive Paget's disease of long standing, but I have observed Paget's sarcoma of the calvarium in a patient who presented no clear roentgen evidence of Paget's disease in any bones other than the calvarium. Commonly it is some one bone that manifests malignant change through the appearance roentgenographically of an ominous rarefied defect that had not been previously noted. However it is not at all unusual to observe the development of two or more sarcomas, more or less simultaneously within bones transformed by Paget's disease, e.g., in the calvarium, and in one or more of the large limb bones, particularly the femur and tibia.

When bone sarcoma supervenes in the course of Paget's disease, it frequently is of the nature of an osteogenic sarcoma. It is perhaps not generally appreciated, however that the sarcoma need not necessarily be osteogenic. In fact, it is not unusual under these circumstances to find, on pathologic examination, that the neoplasm in question represents a fibrosarcoma, or a sarcoma whose stroma is so anaplastic and replete with tumor giant cells as to simulate a malignant giant-cell tumor Whether the latter tumor should actually be regarded as a malignant giant-cell tumor of bone, as Russell has contended is debatable however It is pertinent to note that the development of chondrosarcoma in Paget bone has also been observed,[14] although this appears to be distinctly unusual.

The question is often raised as to the precise incidence of sarcoma complicating Paget's disease, and it is rather difficult to answer satisfactorily because of the necessarily limited experience of any one observer and the inaccuracies inherent in pooled material culled from the literature. Moreover as Schmorl has demonstrated, most cases of Paget's disease show limited skeletal involvement and go unrecognized clinically the changes being confined to portions of the sacrum, or to one or a few lumbar vertebral bodies. However if one considers only cases of more or less extensive, advanced Paget's disease, the usually cited estimate of approximately 10 to 15 per cent seems plausible. The prognosis in such cases is

distinctly bad, and I have no personal knowledge of a single instance of 5-year survival. At the time our bone sarcoma cases were surveyed, there were 7 instances of Paget's sarcoma among them, and follow up observations showed that all had terminated fatally within 6 months of the time of initial observation.



Fig 113—*A* Roentgenogram showing multicentric foci of sclerosing osteogenic sarcoma in the right iliac bone of an older man with advanced Paget's disease. The patient succumbed shortly after attempted resection. *B* Roentgenogram of a sagittal section of one of the tumors in the ilium which also shows coarse trabecular alteration indicative of Paget's disease.

Osteogenic Sarcoma Developing in Multicentric Foci

Brief mention should be made, in passing, of certain rare, but undoubted instances of osteogenic sarcomatosis, in which many or even innumerable tumors develop apparently simultaneously throughout the skeleton. An extraordinary case in point is that reported by Silverman, which I had occasion to witness at autopsy. Literally hundreds of separate tumors of the nature of osteogenic sarcoma, many of them still quite small were found developing within all parts of the skeleton examined. Through the courtesy of Dr E LeMoncheck of Los Angeles I have observed another proved comparable instance in a boy 15 years of age who presented many foci of sclerosing osteogenic sarcoma in the calvarium, vertebral column, and long bones, and whose lung fields were "snowballed" by radiopaque metastases. Dr G L Kraft of this city has called my attention to still another similar case of osteogenic sarcoma apparently developing in multicentric foci (Figs. 114 and 115). Through the courtesy of Dr B W Drompp of Lincoln, Nebraska, I have observed

material from an extraordinary case (to be published) in which the development of an osteogenic sarcoma in a phalanx of a finger was followed some 3 years later by the appearance of a second osteogenic sarcoma in a phalanx of finger of the opposite hand. Continuing, Dr Roy I Peck of Philadelphia has over the past 15 years collected a sizeable group of cases exhibiting multicentric osteogenic sarcoma (as yet unpublished). Also worth citing here is a case of multifocal osteogenic sarcoma reported recently by Price and Truscott in which tumor growth was relatively slow and had not given rise to pulmonary metastases. In their paper these authors mention



Fig 114 —Roentgenogram of an unusual multicentric osteogenic sarcoma. (Courtesy of Dr George Kraft, Los Angeles.)

a few additional relevant case reports in the literature. Altogether it would appear that osteogenic sarcoma developing in multicentric foci is not as rare as one might imagine, although relatively little has been published on the subject.

In none of the instances cited had there been any exposure to radium or other radioactive substances as a predisposing factor.[6,9] Incidentally it may be noted in passing that osteogenic sarcoma has been induced experimentally by feeding radium (to rats) by exposure to plutonium (in rats) and to radiostrontium (in mice) and



Fig 115.—A B and C Additional roentgenograms from the case illustrated in Fig 114 showing numerous discrete foci of sclerosing osteogenic sarcoma, some of them still quite small in the limb bones of both lower extremities.

even by embedding certain irritant plastics beneath the fascia of the anterior abdominal wall of rodents. The development of osteogenic sarcoma in a human being following roentgen irradiation, after a latent interval which may be as short as 3 years or as long as 20 to 30 years or more, may be regarded in a sense as the result of unplanned clinical experiments. To the growing list of such cases in the

Fig 116.—*A* and *B* Roentgenograms of an osteogenic sarcoma originating in a scapula, showing rapid progression over a period of several months.

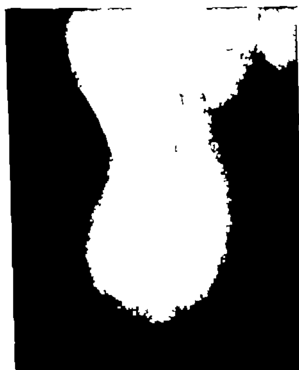


Fig. 117.—Roentgenogram showing recurrence of osteogenic sarcoma in an amputation stump. This complication is not observed with sufficient frequency to justify routine disarticulation at the hip for tumors in the lower femur.

literature, I may add mention of two noteworthy instances at this time one in which osteogenic sarcoma of a *lower rib appeared 20 years after irradiation of a Wilm's tumor* and another in which a focus of extraskeletal osteogenic sarcoma appeared in the skin and subcutis of the cheek some 30 years after x ray irradiation of the affected site (the dosage employed is not known)

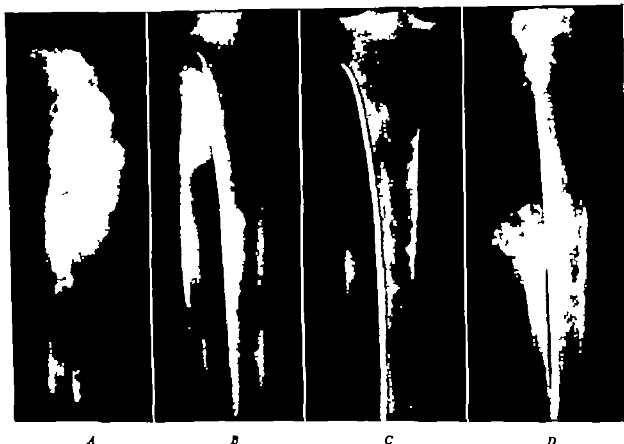
Treatment and Prognosis

Osteogenic sarcoma has an extremely high mortality rate, in spite of prompt radical surgery Radiation therapy even in high dosage, will not effect substantial tumor necrosis, and may even be of limited value in the palliation of distressing pain. Even when ablation or radical resection is resorted to as soon as the diagnosis is established, the prognosis is nevertheless serious, and my experience leads me to believe that the 5-year survival rate is probably no higher than 10 per cent. This impression is based upon a follow up survey of some 25 proved cases of osteogenic sarcoma, which showed only 2 survivors at 5 years or more, although a few additional patients were still alive after 2 or 3 years at the time the survey was made. The great majority had died of pulmonary metastases within 2 years, and often within several months of the time they first came under surgical treatment. The inferences drawn from this survey have been amply confirmed by subsequent experience with a rather large number of pertinent cases.

It is true that there have been other surveys reported in the literature, in which the estimated 5 year survival rate was 20 or 30 per cent, or even higher However there is good reason to infer that these more optimistic impressions are based upon the inclusion in the reported case material of lesions other than osteogenic sarcoma and, specifically of non malignant bone-forming lesions mistaken for osteogenic sarcoma (fibrous dysplasia of bone, myositis ossificans, periosteal ossification, etc.) as well as of neoplasms less serious than osteogenic sarcoma proper (fibrosarcoma and chondrosarcoma particularly) In this same connection, it is pertinent to comment upon the much-discussed paper by Ferguson who after surveying the cases diagnosed as osteogenic sarcoma in the Bone Sarcoma Registry came to the rather curious conclusion that the clinical results in patients operated upon after a delay of 6 months or more were significantly better than in those operated upon promptly Here again, one is forced to suspect that the recorded impressions in regard to diagnosis in the Registry stand in need of critical review and that the cases which terminated fatally in spite of prompt surgery were apparently genuine osteogenic sarcomas, whereas many of those in which delay of 6 months or more was feasible may well have represented other lesions less serious than osteogenic sarcoma. This view is supported by the finding of Budd and MacDonald that of some 118 five-year cures of osteogenic sarcoma, so-called, in the files of the Bone Sarcoma Registry no more than 14 (12 per cent) were actually bone producing sarcomas, whereas 93 (almost 80 per cent) appeared to represent instances of either chondrosarcoma or fibrosarcoma.

The discouraging outlook in dealing with osteogenic sarcoma does not appear to be attributable to any significant delay in its clinical recognition. What seems more probable, unfortunately is that many patients with osteogenic sarcoma already

have pulmonary seeding by the time they present themselves for treatment, even though their chest films appear negative It frequently takes several or many months for these metastases to attain sufficient size and radiopacity for their discernment, and it is apparently only in an occasional instance that pulmonary metastasis fails to develop early or having taken place is followed by regression of the tumor transplants (Figs. 119 and 120) Pulmonary spread usually ensues without apparent involvement of large intermediate veins, although in one of the cases in our hospital



A *B* *C* *D*

Fig 118.—Roentgenograms demonstrating the futility of local resection for osteogenic sarcoma except as a palliative measure. (The patient in this instance refused amputation.) *A* Roentgenogram of the resected specimen. *B* The initial film showing a sclerosing osteogenic sarcoma in the upper end of a fibula. *C* Film taken 9 months after resection showing recurrence in the stump of the fibula. *D* Film taken 15 months postoperatively showing recurrent tumor at the upper as well as the lower end of the excision. Pulmonary metastases were already evident at this time.

files a large tumor thrombus was found in the inferior vena cava (at necropsy) in proximity to an osteogenic sarcoma which had extended well beyond the confines of the iliac bone of origin.

Nevertheless, I am not inclined to take a defeatist attitude, and as long as there is any likelihood of cure following amputation or radical resection, limited though it may be I will continue to recommend it as the only hope for survival.



Fig 119 —*A* Roentgenogram of an amputation specimen showing a sclerosing osteogenic sarcoma in the lower end of a femur *B* Photograph showing massive pulmonary metastasis as observed at autopsy less than a year later Some of the tumor foci have undergone cystic softening. *C* Roentgenogram in another comparable instance showing relatively early pulmo-

The possibility of benefit from lobectomy or pneumonectomy in selected cases showing early limited metastasis must also be borne in mind. In regard to cases in which ablation is contemplated it is important to emphasize again that one should always insist upon confirmation of the clinical and roentgen impression of osteogenic sarcoma by biopsy however clear the diagnosis may seem. It is usually not necessary to incise the tumor widely or to enter the medullary cavity in order to obtain a satisfactory specimen. It is by no means unusual for cases of exuberant callus due to whatever cause of active myositis ossificans, and of periosteal ossification particularly to be mistaken clinically and even pathologically for instances of osteogenic sarcoma, and this probem of differential diagnosis will be dealt with in a later chapter.



Fig. 120.—*A* Roentgenogram showing local recurrence of osteogenic sarcoma following resection of the mandible. *B* Roentgenogram of the lungs in this case showing extensive metastatic foci of sclerosing osteogenic sarcoma, as observed at autopsy some months later. *C* A focus of osteogenic sarcoma encountered within a lumbar vertebral body in this case. (Additional small tumor foci were also observed in the body of the sternum and in one of the ribs examined.)

In principle, amputation should be performed proximal to the bone involved rather than through it, since recurrent osteogenic sarcoma in an amputation stump is sometimes observed (Fig 117). However in dealing with osteogenic sarcoma in the lower end of the femur by far the commonest site of localization, there is little empirical evidence to indicate that disarticulation at the hip is more effective than mid thigh or high thigh amputation.

The problem of devising means to reduce the appallingly high mortality in osteogenic sarcoma continues to be of grave concern. Little, if anything, is gained by unnecessarily drastic surgery since this does not alter the incidence of pulmonary spread. Nor does it seem logical to delay surgery pending intense irradiation of the tumor site, as some have advocated. Even if one could effectively destroy the tumor in this way, which is doubtful, the procedure is tantamount to locking the barn door after the horse has been stolen. With this in mind, I recently advocated supplementing radical surgery by irradiation of both lung fields through multiple ports as an experimental therapeutic procedure in the hope of destroying microscopic tumor foci before they become encased in a coat of armor, or at least reducing the spread to one or two metastatic sites that might be dealt with by segmental or lobar resection. That this is feasible is evidenced by the case reported by Goldenberg[7] in which lobectomy for a solitary pulmonary metastasis from osteogenic sarcoma was followed by 5-year survival. The stakes are sufficiently high to make it worth incurring the possible hazard of post-irradiation pulmonary fibrosis in the event of survival, as a calculated risk.

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XVI

Fibrosarcoma of Bone

Fibrosarcoma of bone, as distinct from osteogenic sarcoma, may be defined as a primary malignant fibroblastic tumor which, upon thorough histologic sampling, fails to exhibit any tendency to form tumor osteoid and bone, either in its local growth or in its metastases. It is distinctly less frequent than osteogenic sarcoma or chondrosarcoma, and I have occasion to see no more than one a year on the average. The tumor usually starts its development within the interior of the affected bone, commonly a large limb bone. The lower end of the femur appears to be its most frequent site, although I have also observed pertinent tumors elsewhere, in the tibia and the humerus, for example. Like osteogenic sarcoma and central chondrosarcoma, central fibrosarcoma of bone tends eventually to penetrate the overlying cortex and extend into the contiguous periosteum and muscle. When it does so it must be distinguished from the occasional fibrosarcoma which arises parosteally and invades the interior of the contiguous bone secondarily by direct extension.

In the light of my personal experience, I cannot accept the categorical statement made by Geschickter and, surprisingly enough, endorsed by Stout to the effect that there are no endosteal (sic) fibrosarcomas but only those which start in the periosteum or parosteal tissues. Nor can I accept their collateral contention that all the cases of apparent endosteal fibrosarcoma of bone represent either osteogenic sarcomas or chondrosarcomas without convincing evidence of differentiation. I am, of course, not alone in dissenting from this extreme view. As previously noted, Budd and MacDonald have advocated the separation of (central) fibrosarcoma from osteogenic sarcoma proper ("osteosarcoma") as a distinctly less serious malignant neoplasm, pointing out that (as of 1943) such tumors accounted for 31 per cent of the 5-year cures of so-called osteogenic sarcoma filed in the Registry of Bone Sarcoma. Phemister also accepted the concept of fibrosarcoma as a distinctive neoplasm of bone, emphasizing that it is much more frequently primary in the medullary region than in the periosteum and that the tumor tissue does not form bone, although periosteal new bone may be laid down in consequence of cortical perforation and pathologic fracture. Coley likewise speaks of medullary

fibrosarcoma as distinct from osteogenic sarcoma,—although I do not agree with him that such neoplasms are necessarily or invariably slowly growing and of low-grade malignancy. This aspect will be discussed presently.

It is relevant at this point to comment briefly upon the comparatively uncommon fibroblastic tumors which appear to arise from the periosteum and produce a slowly enlarging circumscribed, ovoid-shaped mass intimately attached to the external surface of the affected bone. When they have attained appreciable size prior to surgical intervention, these periosteal tumors may sometimes erode the underlying cortical bone, although they do not, as a rule, invade the medullary

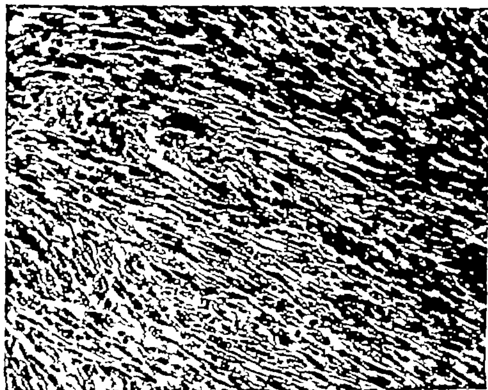


Fig. 121.—Photomicrograph of one of the more cellular fields in a periosteal fibrosarcoma developing on the shaft of a femur. As indicated, the clinical behavior of such tumors is more favorable than their cytology would lead one to expect. In this particular instance the surgeon was not confident of his ability to clear the neoplasm by local resection and elected to amputate. (×220)

cavity. Stout has collected 13 such fibroblastic tumors, of which 8 developed on bones other than large limb bones, notably the scapula, the mandible, and the sacrum and coccyx. He is inclined to regard them as relatively benign neoplasms, inasmuch as metastasis was observed in only 1 of his 13 cases. The relatively few periosteal fibrosarcomas that I have seen have been tumors of rather low-grade malignancy exhibiting a tendency to relatively slow growth, a singular lack of conspicuous pleomorphism of their connective tissue stroma histologically, and a disposition to merely local recurrence after incomplete surgical extirpation. (Fig. 121)

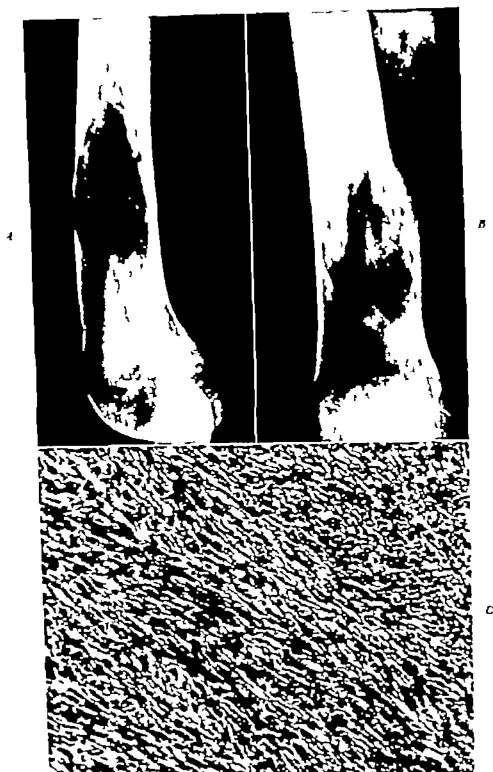


Fig 122.—*A* and *B* Roentgenograms of a primary malignant neoplasm in the lower shaft of the femur of an older adult, which on biopsy proved to be a fibrosarcoma. Amputation was carried out promptly From the x ray picture alone one might suspect the presence of a primary sarcoma, though not necessarily fibrosarcoma. *C* Photomicrograph of the fibrosarcoma illustrated above, as observed in the biopsy specimen. (×200.)

Central (or medullary) fibrosarcomas of bone, on the other hand, show such wide variation in growth potential and aggressiveness that facile generalizations in regard to them hardly seem justified. Their clinical behavior is usually though not invariably reflected in their cytologic appearance. At one extreme, there are highly malignant fibroblastic neoplasms which by virtue of their rapid and aggressive growth, their ominous cytology (reflected in moderate anaplasia, cell irregularity and rather numerous mitotic figures) and their tendency to early pulmonary metastasis behave not unlike osteogenic sarcomas, though failing to exhibit any



Fig 123—*A* Photograph of a central fibrosarcoma in the lower end of the femur of an adult. The cortical defect represents the biopsy site. The neoplastic tissue showed extensive old hemorrhage and necrosis. This tumor developed relatively slowly over a period of several years and then took on a spurt of growth reflected in its cytologic picture (see Fig 127 *A*). Nowhere in any of the numerous fields examined was there evidence of tumor osteoid or new bone formation. *B* X ray picture of the amputation specimen shown in *A*. *C* X ray picture of the same specimen taken after all of the tumor tissue had been carefully scooped out leaving only the surrounding bony shell. This demonstrates convincingly that the trabeculated pattern observed in *B* reflects endosteal reaction to the slowly expanding tumor.

tendency whatever to form tumor osteoid and bone, even upon the most searching histologic examination of entire amputation specimens. At most, one observes scattered small focal areas of hyalinization and calcification, just as one may in fibroblastic meningiomas for example There are still some who feel that such neoplasms should be regarded as osteogenic sarcomas which have not manifested their osteogenic potentiality but this concept hardly seems to make good sense as a practical working hypothesis. In my opinion a neoplasm should be appraised in the light of what it does and what it actually looks like, rather than by any preconceived notion in regard to what it might do under other circumstances. In dealing clinically with such neoplasms, the outlook is serious in spite of prompt radical surgery and one must be guarded in the matter of prognosis.

To continue there are additional less serious central fibrosarcomas of bone which as others have pointed out also,[1,2,3,4] develop more slowly although they eventually break through the cortex of the affected bone This sequence of events seems clear when one follows the evolution of such tumors roentgenographically and I am at a loss to understand why Geschickter and Stout insist that the reverse necessarily holds. It is true, as noted, that sarcomas of one kind or another (of fascial, nerve, muscle or vascular origin) arising not within the bone but in proximity to it, may occasionally as they attain appreciable size destroy the contiguous cortex and invade the bone by direct extension. Such extra-osseous or parosteal sarcomas, however are not the subject of the present discussion.

In dealing surgically with the less serious central fibrosarcomas, any procedure short of amputation is likely to be unsuccessful, although an occasional early tumor particularly in a child, may be considered suitable for block resection and reconstruction with the aid of large bone grafts. As a rule attempts at conservative surgery seeking to avoid ablation are usually followed by obvious local recurrence. Such tumors tend eventually to metastasize to the lungs particularly but they are rather slow to do so as compared with osteogenic sarcoma, and therefore lend themselves to cure by ablation at an appropriate level, if one does not temporize indefinitely.

At the other extreme of the gamut, one occasionally encounters still other tumors whose cytology makes a diagnosis of fibrosarcoma mandatory by the usual criteria, but which are nevertheless surprisingly indolent in their growth. In fact, such neoplasms may show relatively little progress over a period of clinical and roentgenographic observation of several years or more. I have knowledge of a tumor in point, situated in the mid-shaft of the tibia of an older adult, which did not manifest appreciable activity until 10 years after its presence was recognized (review of the original biopsy specimen clearly showed fibrosarcoma) It should be emphasized however that even these favorable central fibrosarcomas are not to be regarded too lightly since they may at any time take on a spurt of growth and become aggressive

Since the first edition of this book appeared, I have had occasion to observe material from no more than six clear-cut primary fibrosarcomas of bone (several other possible instances in which the diagnosis was in question for one reason or another will not be discussed here) Four of these tumors were rather conventional

and were encountered in either the femoral or tibial shafts of older adults. It is interesting to note that in none of them was the diagnosis of fibrosarcoma suspected clinically prior to tissue examination. Amputation at an appropriate level was resorted to in each instance, but not enough time has elapsed to judge whether cures were obtained. Another developed in the upper end of the humerus of a comparatively young man 31 years of age, who was treated twice for ostensible bone



Fig. 124.



Fig. 125.

Fig. 124.—Roentgenogram of a large lytic lesion in the upper end of the humerus of a 31-year-old man. The cortical and intramedullary dissolution (not evident in previous x-ray films) proved to be due to the presence of a fibrosarcoma. The circumstances pertaining to the case strongly suggested that this tumor may well have developed within an old solitary unicameral bone cyst.

Fig. 125.—Roentgenogram showing an advanced, destructive tumor in the lower end of a femur which proved to be fibrosarcoma. This site had been irradiated some years previously for another condition (total dosage is not known). The subsequent clinical course was featured by amputation after considerable delay, recurrence in the stump, and eventual spread to other bones and soft parts.

cyst by curettement and packing with bone chips before the presence of sarcoma was recognized. The location of the lesion, the youthfulness of the patient, and certain features of the tissue reaction, notably the presence of abundant old lipid deposits, did in fact suggest origin of the tumor within an old bone cyst (Fig. 124). The last instance developed within a cuboid bone (in a 60-year-old man)

material from which also showed the presence of chronic sclerosing osteomyelitis. This lesion was at first thought to be benign and was treated by curettement and the insertion of a bone graft. It was not until the graft was later resorbed and the roentgen films showed destructive changes that misgivings arose. It is entirely possible that the infection in the bone was a predisposing factor in the development of fibrosarcoma, but this cannot be proved conclusively.



A. B.

Fig. 126.—*A*, Roentgenogram of a primary malignant neoplasm in the upper end of the humerus of an older woman, which proved on biopsy to represent a fibrosarcoma (see Fig. 127 *B*). Despite ablation this patient developed metastases within a few months. Examination of the cortical bone in the head and upper shaft of the humerus revealed the presence of Paget's disease. *B*, Roentgenogram of the amputation specimen (reduced) showing the lytic tumor defect and perforation of the cortex (this developed after the film shown in *A* was taken) as well as changes in the humerus incidental to Paget's disease (these changes, of course, were more clearly seen in the original).

Clearly this remarkably interesting group of fibroblastic neoplasms calls for further study and exploration, but in view of the limited relevant material available, I must be content at this time with pointing out some of the problems involved. It is pertinent here to mention also the possibility that some of the central fibrosar

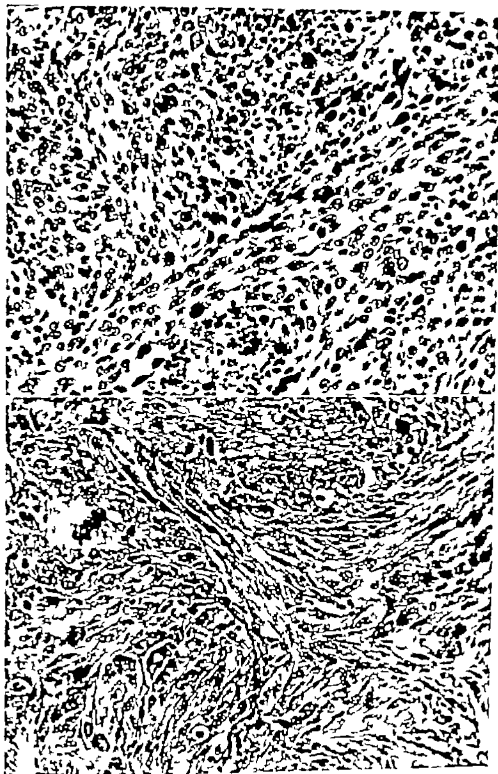


Fig. 127.—*A*, Photomicrograph of the fibrosarcoma illustrated in Fig. 125. (×220) *B*, Photomicrograph of the fibrosarcoma complicating Paget's disease of the humerus illustrated in Fig. 126. The anaplasia and formation of tumor giant cells are features commonly associated with Paget's sarcoma. (×200)

comas, so-called may conceivably represent malignant Schwannian tumors, although this is still a moot point. It should be noted further as is well known, that when sarcoma develops within Paget bone it may be of the nature of fibrosarcoma rather than osteogenic sarcoma (Fig 126) and this applies to post irradiation sarcoma, as well.

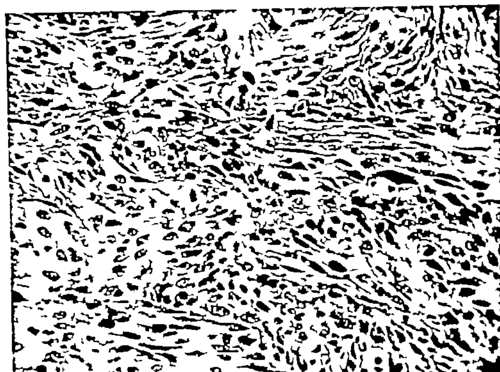


Fig. 128—Photomicrograph showing a representative field of a post irradiation fibrosarcoma developing in the upper humerus of a child and necessitating disarticulation. This site had been heavily irradiated some years previously (without prior biopsy) on the premise that a giant-cell tumor was present. Actually review of the x ray films indicated that the lesion initially was, in all probability a solitary unicameral bone cyst. (X220)

Inasmuch as the roentgen appearance of any particular fibrosarcoma is likely to be rather ambiguous, a definitive diagnosis of fibrosarcoma can hardly be ventured with assurance, although one may perhaps suspect the presence of a primary sarcoma from the moth-eaten or mottled rarefaction of the affected bone area (usually the end of a long bone) This impression is likely to be heightened if there has been some destruction of the cortex and especially if there is evidence as well of periosteal new bone formation at the site of the lesion. Even when it seems clear from the roentgenographic picture that the lesion probably represents a primary malignant tumor biopsy is required to define the precise nature of the tumor as a basis for treatment and prognosis. In evaluating such a biopsy specimen, one must, of course be circumspect about the possibility that one is dealing with an unossified peripheral area of an osteolytic osteogenic sarcoma.



Fig 129—*A* Amputation specimen showing a far advanced fibrosarcoma developing in a femur The cellular neoplasm has destroyed the cortex over a wide area and extensively invaded the surrounding soft parts *B* Photomicrograph of this subject (at autopsy) showing massive recurrence of tumor at the site of disarticulation.



Fig 130—*A* Photograph of an amputation specimen showing another advanced fibrosarcoma situated in the lower end of a femur (a favorite site of localization) As in the instance illustrated in Fig 129 *A* this neoplasm has also destroyed much of the shaft of the affected femur and extended well beyond the confines of the bone. *B* Photograph of the patient's knee region before operation, showing conspicuous tumorous swelling

Multicentric Fibrosarcomas of Bone

In the discussion of osteogenic sarcoma it was pointed out that in certain rare instances multiple tumors may develop apparently independently and more or less simultaneously over the entire skeleton. It would appear from the extraordinary case reported by Steiner that, similarly, multicentric tumors of the nature of fibrosarcoma may develop within the skeleton as well as the visceral soft parts, as an expression of a peculiar generalized fibrosarcomatosis (unrelated to either Paget's disease or Recklinghausen's neurofibromatosis). The point is of greater academic interest than of practical moment, however, and for further details the reader is referred to the original paper.

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XVII

Ewing's Sarcoma of Bone

With the passing of time, I have become more convinced than ever that there are valid and useful pathologic as well as clinical grounds for making a clear distinction between Ewing's tumor and primary reticulum-cell sarcoma (of bone marrow) So far as the patient is concerned, it means a difference between a survival rate of 5 per cent (or less) and one of 50 per cent. The fact that this distinction may not be easy in actual practice where one is dealing with meager biopsy specimens showing extensive degeneration or necrosis does not negate the general principle. Today one no longer needs to be on the defensive or feel apologetic about believing in the existenc of Ewing's tumor as a rather primitive, multicentric *primary malignant tumor of bone, different from other marrow tumors* and distinguishable from certain metastatic neoplasms in bone which may on occasion mimic it cytologically notably neuroblastoma and undifferentiated round-cell carcinoma. In this connection it may be remarked that genuine Ewing's sarcoma is not commonly encountered (I have observed material from no more than 10 cases within the past 5 years) and it is freely conceded, as Willis has maintained, that in the past the diagnosis has been often applied uncritically to instances of other tumors and probably still is, though less often.

For 20 years or more following Ewing's original pertinent papers (under the titles of "diffuse endothelioma of bone" and "endothelial myeloma of bone," respectively) the subject was one of the most controversial in the field of bone tumors, and it may be added that much of the confusion resulted from the fact that some of the things that Ewing and his disciples had stated were inaccurate and misleading That this should be so is not too surprising since any attempt to classify neoplasms of more or less undifferentiated round-cell cytology entails many subtleties in differential diagnosis in regard to which there is as yet no unanimity of opinion. Positive identification from biopsy specimens alone is particularly difficult all the more so since the tumor tissue is peculiarly prone to undergo degeneration (manifested usually in shrinkage of tumor cells and distortion otherwise of their cytologic details) necrosis, and secondary leukocytic reaction. If in addition, the tumor

in question has been irradiated prior to biopsy as is sometimes the case, it may be virtually impossible to determine its probable nature. Even when pertinent cases are followed to autopsy the validity of a final opinion of Ewing's sarcoma depends largely upon the skill and thoroughness with which the prosector has searched for other neoplasms of round-cell cytology particularly neuroblastoma, undifferentiated carcinoma extensively metastatic to the skeleton from a small cryptic primary focus, malignant lymphoma involving bone marrow predominantly and, on occasion, even multiple myeloma.

The relevant clinical features that Ewing stressed as being important in the delineation of the neoplasm that now bears his name have not proved to be very specific, although it should be noted that Coley, Higinbotham and Bowden in a comparatively recent survey apparently still accept their diagnostic value. These features were essentially youthfulness of the patients, a rather characteristic roentgenographic appearance of the presenting bone lesion, a gratifying response of this lesion to radiation therapy, and eventually (in all but a few cases) the appearance of lesions in other bones and especially in the lungs, with fatal outcome. The age factor certainly is not decisive. The roentgen picture is not either and, on the whole, it reflects destruction of the affected bone area, along with evidence of periosteal new bone formation if the tumor has already perforated the cortex. Gratifying response to x ray therapy locally is not specific either inasmuch as reticulum-cell sarcoma, for instance, may be very vulnerable to irradiation. Finally eventual widespread dissemination throughout the skeleton and pulmonary metastases are not peculiar to any one neoplasm in particular It is not surprising therefore, that the concept of Ewing's sarcoma as outlined has been subjected to criticism and certain modifications. Some investigators have even doubted the validity of the basic concept itself pointing out that it had been founded on and largely sustained by clinical and biopsy findings, rather than on the study of cases followed to their termination and systematically autopsied. In relation to diagnosis, so much faith has long reposed in the clinical aspects as sketched here that, summarized as constituting "Ewing's syndrome," they often took precedence over tissue examination in arriving at a diagnosis—a point of view which has proved itself unjustified. Many including Neely and Rogers, Swenson, and Barden, have pointed out that the roentgenographic picture in itself is not sufficiently characteristic for the condition to be of reliable diagnostic value. Colville and Willis also emphasized the pitfalls involved in arriving at a diagnosis even through biopsy and the diagnostic surprise frequently encountered when a case suspected of being Ewing's sarcoma is finally subjected to detailed post mortem examination.

In 1947 in collaboration with Jaffe, I had occasion to survey the relevant hospital material pertaining to cases which had been diagnosed as Ewing's tumor during the preceding 20 years. In keeping with the general experience, we found that that diagnosis had been applied somewhat uncritically to a substantial number of biopsied lesions which appeared on review actually to represent instances of neuroblastoma, carcinoma, lymphosarcoma, and multiple myeloma. In other instances, the quality of the biopsy specimens was such that we were reluctant to venture any definitive diagnosis beyond that of a malignant neoplasm. After eliminating all

these, there remained, however a hard core of some 17 specimens presenting consistently uniform cytology (at least in fields that were well preserved) which could not be readily disposed of as instances of any of the tumors mentioned. In 4 of these instances the impressions gained from the biopsy specimens were substantiated by complete examination at autopsy These tumors were composed of a compact network of cells with ill-defined borders, meager cytoplasm and fairly large and uniform, prominent, round or oval nuclei showing scattered chromatin.*

From this undifferentiated cytologic pattern I am inclined to infer as a working hypothesis, that the tumor cells of Ewing's sarcoma are apparently derived from the mesenchymal connective tissue framework of the bone marrow I have not been impressed by the cytologic evidence advanced by Ewing and his disciples in support of the idea that the tumor cells are derived from angio-endothelium, nor have I found in my own material that perivascular orientation of the tumor cells and the presence of pseudorosettes constitute significant features of the cytologic picture.

It is here that we come to the nub of the controversy in regard to the nature of what has been called Ewing's tumor Barring those who still seek to defend Ewing's theory of histogenesis, there appears to be substantial agreement among pathologists who have investigated the problem that the tumor (seen in its intact, well-preserved state) does have some resemblance cytologically to reticulum-cell sarcoma of the bone marrow Does Ewing's tumor then actually represent a type of reticulum-cell sarcoma? Or since resemblance may fall short of identity does it conceivably represent a separate neoplasm which, though of reticular origin, has followed a distinct line of differentiation away from the multipotent parent reticulum cells? Oberling conceives of and designates Ewing's sarcoma as a reticulosarcoma of bone marrow and also believes in the kinship between the latter and the generally recognized reticulosarcoma of lymph nodes. Willis also has been skeptical of the existence of Ewing's sarcoma in the sense of a separate and distinct, independent neoplasm.

Along the same line of thought, Stout stated candidly (1943) that he is not at *all sure he* can distinguish Ewing's tumor from reticulum-cell sarcoma and has expressed his uncertainty as to what should properly be called Ewing's tumor While altogether sympathetic to this view I feel that the two neoplasms can be distinguished cytologically although the distinction is sometimes a rather subtle one. In recent years my colleagues and I have independently scrutinized current slides presenting this problem in differentiation and find that our impressions are in substantial agreement. As practical cues to the recognition of Ewing tumors one may stress the great uniformity of the compact tumor cells the absence of distinct cell boundaries making for an apparent syncytium of naked nuclei, and the presence of finely divided or powdery chromatin within the nucleus tending to give it a relatively dark, often smokey appearance (as compared with that of neo-

* It is relevant here to point out that Ewing's own description of the cell type of the lesion as small polyhedral cell with pale cytoplasm, small hyperchromatic nucleus, and well-defined cell border apparently has reference to degenerated, shrunken, and otherwise modified fields, observed not infrequently in biopsy specimens. If Ewing actually followed any of his reported cases to autopsy he made no mention of the pertinent findings in any of his papers on the subject, surprising as that may seem.

plastic reticulum cells) and, conversely the absence of any reniform nuclei and the lack of evidence of histiocytic or phagocytic activity Quite apart from any consideration of their comparative cytology however there are significant differences in the natural history and clinical behavior of Ewing's tumor and primary reticulum-cell sarcoma of bone, as emphasized by Parker and Jackson, and others (see also page 296) For these reasons I prefer to use the neutral name of Ewing's sarcoma for the tumor under discussion, avoiding any confusing nosologic reference to its possible reticular origin.

Be that as it may the clinician responsible for the actual management of a relevant case is not overly preoccupied with theoretical considerations in regard to histogenesis, but is more concerned with specific problems in diagnosis and therapy For the purpose of outlining the pertinent clinical features, I will rely mainly upon observations gleaned from analysis of my own case material, although, with minor variations, these are essentially in accord with those remarked upon in other comparable surveys.

Clinical Features

Age and Sex Incidence.—Ewing's sarcoma is most commonly observed in adolescents or young adults, that is, in the age group between 10 and 25 years, although an occasional instance may be seen in a younger child or an older adult. However in considering the age factor in differential diagnosis, one should bear in mind that in young children, particularly neuroblastoma is a strong possibility that in adults past 35 or 40 years, metastatic carcinoma must be suspected and that in older adults past 50 years, multiple myeloma also becomes a major possibility

The majority of patients are likely to be males, although this difference in sex incidence was not as strikingly reflected in our material as it is in the series of cases reported by Coley and his colleagues, for example.

Localization.—In most instances, only a single skeletal lesion was clinically recognized and demonstrated roentgenographically at the time of the patient's admission to the hospital. In an occasional case, however roentgenographic examination of the rest of the skeleton already revealed one or more additional (clinically silent) foci of bone involvement or even early pulmonary metastases. The presenting lesions were commonly situated in trunk bones, as well as in the long limb bones, e.g., in one or another part of an innominate bone, a rib a scapula, a clavicle, or a vertebra. In so far as the limb bones are concerned, it is usually the shaft rather than the end of the bone that is affected. Also, while the large bones are often involved (the femur tibia, and humerus, particularly) it is rather surprising how often the fibula is the site of the presenting tumor

Clinical Findings.—In regard to the role of trauma as a possible instigating factor it may be said that analysis of our data did not furnish any convincing evidence in favor of a causal relationship between trauma and the development of a Ewing's sarcoma.

Survey of the clinical histories of the patients in our series shows that pain was the one consistent complaint. With few exceptions, the pain was of at least

some months standing and in several cases it had been present for at least one year before admission. In most instances, it had become increasingly severe and persistent during some weeks or months immediately before admission. Along with the local pain, there were often complaints related to spread of the tumor beyond the limits of the affected bone and varying with the location of the presenting lesion. For instance patients in whom some part of an innominate bone was involved usually complained of disability relating to the hip joint and sometimes also of radiating pain down the lower limb. In connection with presenting lesions near the end of a long bone there were sometimes complaints of lameness or stiffness of the corresponding joint, and, in one case in which the lesion was situated near the lower end of the femur there were repeated serous effusions into the knee joint. In cases in which the presenting lesion was in a lumbar vertebra, there were, in addition to the local pain, complaints ascribable to implication of nerve trunks in the area, such as pain radiating down the limbs, and tingling sensations and weakness in the leg. Location of the presenting lesion in a rib was found associated with pleural effusion in one case. Other locations of the presenting lesion (for instance, in the skull) are associated with their own special clinical disabilities.

Just as local pain was the dominant clinical complaint, so the presence of a local tumor mass was the major clinical finding at the time of initial examination. A more or less prominent tumor mass was palpable at the site of the presenting bone lesion in all but 3 of our 17 cases. This finding emphasizes the strong tendency of Ewing's sarcoma to break out through the cortex of the bone and spread into the surrounding soft tissues. Conspicuously large tumor masses were palpable in cases in which the tumor appeared in an innominate bone. Spreading internally toward the pelvic cavity the tumor could sometimes be palpated as an elastic, irregular globular mass through the rectum if the tumor was low down or in the lower quadrant of the abdomen if it was situated higher up. Spreading externally a tumor springing from an innominate bone sometimes produced a large tumor mass palpable in the groin or in the gluteal region. In one of our cases in which the presenting lesion was in the shaft of a humerus there was likewise a very large extra-osseous tumor mass connected with the bone. When the presenting tumor was in a superficially located bone such as a clavicle or a rib the mass produced by extra-osseous spread could likewise be seen as well as palpated.

Tenderness to pressure at the site of the lesion was recorded in practically all cases. Frequently the subcutaneous veins overlying the presenting lesion were found to be prominent. However it was only occasionally that increased local heat was mentioned in connection with the physical examination.

A survey of the temperature charts and the laboratory findings *in our cases* revealed what appeared to be significant information of clinical value. Many of the patients had been in the hospital for almost a week before *specimens* were secured for biopsy. During this time they had slight fever with daily rises in temperature to about 101° F. These patients also presented a secondary anemia

(with a red blood cell count of about 3,500,000) and sometimes also a leukocytosis. In addition, they usually showed a high sedimentation rate of the blood. Altogether these findings proved to be more significant in judging immediate prognosis than the size of the presenting lesion. Specifically, the patients in whom some fever and secondary anemia were noted had a fulminating course ending in death within a few months after admission to the hospital. On the other hand, those patients who had no fever on admission, and no anemia or increased sedimentation rate, tended to survive for a year or more after admission.

Roentgenographic Findings

Roentgenographic Appearance of the Presenting Bone Lesion.—By the presenting bone lesion is meant, as already indicated, the one causing the complaints which led the patient to enter the hospital. This was often the only lesion discernible even when the entire skeleton was examined. One need only review the presenting lesions in a series of cases to appreciate the difficulty of making a definitive diagnosis of Ewing's sarcoma by x-ray examination alone. If the extent of bone involvement in the presenting lesion is still small and no lesions are found elsewhere, the picture may be misconstrued as that of an inflammatory lesion. However, in most cases the picture of the presenting lesion suggests a malignant tumor, although it may be misinterpreted as some malignant tumor other than Ewing's sarcoma.

The only fairly consistent roentgenographic finding is evidence of destruction or lysis of bone, in itself a rather nondescript feature. In some cases the presenting lesion may appear merely as a small zone of mottled rarefaction reflecting destruction of the spongiosa and, to a lesser degree, of the overlying cortex associated with only a trace of periosteal new bone reaction to the neoplastic tissue which has penetrated the cortex. This picture (which may also include some areas of condensation) is very likely to suggest an inflammatory lesion (pyogenic or tuberculous osteomyelitis) rather than a tumor, although within a month or two one is likely to observe evidence of rapid extension of the pathologic area within and beyond the bone, so that one begins to suspect the presence of a malignant neoplasm. It should be emphasized that, although the early roentgenogram shows only a relatively small area of bone destruction, this cannot be taken to indicate the actual extent of involvement of the bone, the marrow spaces of which may already be riddled by neoplastic tissue.

When the initial roentgenogram of the presenting lesion shows rather clearly that one is dealing with a malignant tumor, one usually notes a large area of bone destruction and often a large overlying soft tissue mass as well. The affected area in the bone may show some expansion, but this is not pronounced. It appears irregularly rarefied and mottled from the presence of smaller or larger foci of relative radiolucency and shows disruption of the cortical outline over a variable distance. Reactive deposition of new bone by the periosteum, where the neoplastic tissue is penetrating the cortex, is very conspicuous.

When the shaft of a *long bone is the site of* Ewing's sarcoma, one does not commonly observe the concentric "onionpeel" layers of laminated periosteal new bone held to be characteristic of the roentgenologic appearance of this tumor. If the observer necessarily expects to find this allegedly pathognomonic sign, he is likely to miss the diagnosis in many cases. Moreover, even when it is present, it



Fig 131.—*A* Roentgenogram of a mottled and rarefied lesion in the upper fibula which proved to be a Ewing's sarcoma. The tumor had not as yet provoked any obvious periosteal reaction. *B* Another, more advanced, Ewing's sarcoma of a femur showing prominent periosteal new bone apposition as a reaction to penetration of the cortex by the neoplasm. The cortical defect represents the biopsy site. Shortly after this film was taken, pulmonary metastases were already in evidence.

is not necessarily indicative of Ewing's sarcoma. It should be noted, also, that occasionally the pattern of periosteal new bone formation in an advanced lesion of Ewing's sarcoma may be that of more or less transverse radiopaque streaks, so that the picture of the destructive bone lesion and of the overlying soft tissue mass may be suggestive of osteogenic sarcoma.

Altogether the only conclusions that can be drawn in regard to the roentgenographic appearance of the presenting lesion are that bone destruction (osteolysis) is the dominant feature of Ewing's sarcoma and that there is no typical appearance for this lesion. In general, Ewing's sarcoma is a tumor difficult to diagnose on a roentgenographic basis, often being mistaken in its early stages for an inflammatory lesion and in its later stages for other malignant tumors,



Fig 132.—*A* Roentgenogram of another vaguely defined pertinent lesion in the upper shaft of a femur which has provoked the formation of delicate perpendicular striations of periosteal new bone only faintly discernible in reproduction. Biopsy showed the lesion to represent a Ewing's sarcoma. *B* Roentgenogram of a destructive lesion in the shaft of the femur of a child, which suggested Ewing's tumor to most observers, although the impression from the biopsy slides was rather that of a metastatic neoplasm, probably neuroblastoma. Cases such as this emphasize again that in the matter of diagnosis of Ewing's sarcoma an unverified roentgen impression may have little validity

including metastatic neoplasms. In many cases it may be quite difficult to make a differential diagnosis on a roentgenographic basis between Ewing's tumor and chondrosarcoma, "osteolytic" osteogenic sarcoma, malignant lymphoma, or metastatic neoplasms (including metastatic neuroblastoma) It should be noted also that a solitary lesion of eosinophilic granuloma of bone may be mistaken for Ewing's sarcoma. To make certain that a suspected tumor is Ewing's sarcoma,

tissue examination is essential, but it must be emphasized that the pathologist may easily be mistaken in his opinion, especially if the tissue available is meager or extensively modified by necrosis and secondary inflammation. However in this connection, the error is more likely to be that of mistaking other lesions (anaplastic carcinoma, metastatic neuroblastoma, malignant lymphoma) for Ewing's sarcoma, than the reverse.

Roentgenographic Appearance of the "Metastatic" Bone Lesions.—Whether the additional lesions found roentgenographically on initial examination, or subsequently represent metastases from the presenting lesion or independent multicentric foci does not concern us here. Roentgenographically these additional lesions, like the presenting lesion, show evidence of lysis of bone. They appear first as rather faint, slightly mottled areas of rarefaction. As the resorption of the bone increases, the small, multiple, roundish foci of rarefaction become more distinct and may merge into larger, more clear-cut areas of radiolucency. In flat bones, such as those of the skull or the ilium, multiple, clear-cut, punched-out areas of rarefaction may appear in consequence of lytic destruction of the spongiosa and overlying cortex. In some instances a pathologic fracture of a long bone from destructive resorption may become manifest. It is important to bear in mind, in any event, that the actual extent of involvement of the skeleton at any one time is never adequately reflected roentgenographically. This is true even in fatal cases in which a number of destructive lesions have been demonstrated roentgenographically in bones other than the one containing the presenting lesion. At autopsy if many additional bones are opened, they too will be found to have been far more extensively invaded than was suspected from roentgenographic study of the skeleton shortly before death.

Pathologic Features

Gross Description.—Our experience supports the idea that Ewing's sarcoma arises in the marrow spaces of the interior of the affected bone, rather than in the Haversian spaces of the cortex or beneath the periosteum. Also, as has been indicated, anatomic examination of an affected bone will reveal much more extensive involvement than the roentgenographic or clinical findings would suggest. This can be effectively demonstrated in cases in which the presenting lesion is in a long bone, which is made available by amputation. In this connection I may cite a pertinent case of a tumor in a femur which roentgenographically seemed to affect only the medial condyle and the adjacent part of the shaft. The cortex in this region was fuzzy and had a superposed soft tissue swelling about 2 cm. in thickness. When this femur was stripped of its surrounding muscles and cut in the frontal plane it showed neoplastic tissue not only in the medial condyle but also in the lateral condyle and contiguous portions of the shaft, in the major marrow cavity and even in the marrow spaces of the spongiosa of the upper end. The neoplastic tissue in the region of the medial condyle and that which had penetrated beyond the cortex in this region was, for the most part, discolored by

hemorrhage and interspersed with yellowish areas due to necrosis of both neoplasm and spongiosa. Elsewhere, for the most part, the neoplastic tissue was not modified by hemorrhage or necrosis, was whitish and, notably in the major marrow cavity took the form of massed, soft, glistening tumor nodules. Thus, the diseased area clearly visible in the pre-amputation roentgenogram of this femur was merely the area in which the changes were most advanced and destructive. Neither the inguinal nor the popliteal lymph nodes were enlarged or involved by tumor Furthermore, in spite of the extensive involvement of the femur no tumor foci were discernible in the tibia, fibula, or bones of the foot, all of which were opened and examined. These negative findings are of interest because at autopsy 3½ months after the disarticulation of the right lower limb widespread involvement of the skeleton and visceral metastases were found.

In contrast to the small extra-osseous tumor mass demonstrated in the femoral lesion just described, one often finds a very large tumor mass extending beyond the limits of the bone as part of the presenting lesion. This was well demonstrated in the case of a young girl whose presenting lesion was in the left ilium and whose complaints were of only a few days standing at the time of admission to the hospital, but who then showed a firm tumor mass of the size of a neonatal head, fixed to the ilium and palpable in the lower quadrant and groin. Although this patient appeared to be in good general health on admission, roentgenograms already showed pulmonary metastases, and she died 4 months later In so far as the presenting lesion was concerned, autopsy revealed a huge mass overlying the inner surface of the left innominate bone, which had pushed the urinary bladder and the genital organs anteriorly and the sigmoid and rectum medially On removal of the left innominate bone, it was found that the tumor had extended posteriorly through the ilium and was bulging into the gluteal muscles and penetrating the capsule of the hip joint. The extra-osseous neoplastic tissue was soft, friable, extensively hemorrhagic, spongy and cystic on the whole, and in many places almost diffluent. The iliac bone was riddled by neoplastic tissue which was cystic in many places and there were many defects in its cortex, both on the inner and outer aspects from which as noted, the tumor had spread beyond the limits of the ilium proper into the surrounding soft tissues.

As previously mentioned, in 4 of the 17 cases upon which this discussion is based autopsy was done These autopsies were carried out with full awareness of the general lack of thorough autopsy studies in cases of Ewing's sarcoma. At the time of death, 2 of the patients were 16 years of age the other 2 patients were 18 and 19 years old, respectively Three were females. The youthfulness of these patients makes it improbable that the skeletal lesions represented metastases from a carcinoma. Moreover if we were dealing in these cases with carcinoma metastases from an unrecognized primary growth, it is highly improbable that these lesions would consistently present the cytologic pattern peculiar to well-preserved Ewing's sarcoma namely cells of rather uniform size, with ill-defined borders, little cytoplasm, and fairly large and rather uniform roundish or oval nuclei showing scattered chromatin.

Also, the findings, at least in the 2 cases (1 male and 1 female) in which we personally did autopsies, clearly ruled out the presence of a hidden carcinoma. The breasts and testes were carefully searched for neoplastic tissue and none was found. In both cases, the lungs were given particular attention. In one no grossly visible tumor nodules were found anywhere in the pulmonary parenchyma. The bronchi, which were opened to the very small branches, as well as the hilar

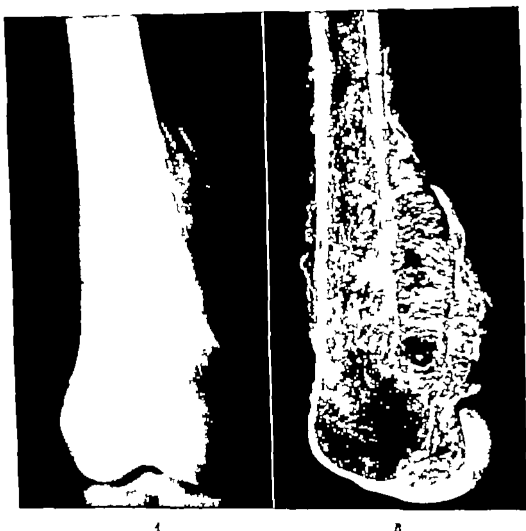


Fig. 133.—*A* Roentgenogram of a Ewing's sarcoma in the lower shaft of a femur of a young woman who had complained of pain and some swelling for many months. Even at this late date, the extent of involvement of the spongiosa and marrow is only vaguely indicated although it is clear from the pattern of periosteal new bone reaction that the neoplasm has already extended well beyond the confines of the cortex. *B* Amputation specimen of the Ewing's sarcoma shown in *A*. The tumor has permeated the cortex over a wide area and has flourished beneath the raised periosteum. Ablation was done in this case with full awareness that it offered only a slim chance for cure. The surgeon elected to amputate through the thigh rather than disarticulate in the hope of utilizing a good prosthesis. Unfortunately examination of the fatty marrow in the shaft at the level of amputation showed the presence of a microscopic focus of tumor

lymph nodes showed no gross evidence of involvement, reducing the likelihood that we had overlooked a primary bronchial carcinoma. In the other case, although all lobes of the lungs were riddled with hundreds of soft, richly cellular largely hemorrhagic and liquefied tumor nodules of various sizes, they showed no single massive tumor and it was plain from their gross appearance that the lesions were metastatic. In the course of the autopsies, full consideration was given to the



Fig 134.—Roentgenogram and photograph of another amputation specimen showing a Ewing's sarcoma which developed in the shaft of a humerus The patient a young man in his twenties, had complained of pain for about 9 months. Dissection of the specimen showed that the tumor was already invading the deltoid muscle at its insertion He remained ostensibly well for over 4 years after disarticulation, but then developed a number of pulmonary metastases which proved fatal despite attempts at local resection of the initial ones.

fact that the gastrointestinal tract, and especially the stomach, can be the site of unsuspected carcinoma, but neither the gastrointestinal tract nor the lymphoid tissue regional to it showed tumorous involvement. In brief every precaution was taken to exclude the possibility that we were dealing not with a tumor primary in the skeleton but merely with metastases to the skeleton from a carcinoma which,

in its primary site, was overlooked because it was inconspicuous or, although observed, was misinterpreted as a metastasis.

In a case thought to represent Ewing's sarcoma the problem posed by neuroblastoma (primary in the adrenal medulla or in sympathetic nervous tissue elsewhere) is an even greater challenge than that raised by carcinoma. Sympathicoblastoma must always be ruled out in such a case, since this tumor not only has a strong tendency to metastasize widely to the skeleton but may bear a confusing cytologic resemblance to Ewing's sarcoma. This point was rightly stressed by Willis, although he has often been misinterpreted as rejecting entirely the entity of Ewing's sarcoma and holding that all such cases represent merely metastases, particularly from neuroblastoma. Be that as it may the adrenals in all 4 of our autopsied cases failed to show on detailed gross examination, evidence of tumorous involvement or of any other abnormality In the 2 cases in which we did autopsies personally an extended search of the areas around the adrenals and of the sympathetic chains along the vertebral column failed to show evidence of an extra adrenal sympathicoblastoma.

As to the viscera, we have already pointed out that the lungs grossly may be found free of neoplastic tissue or on the contrary riddled with metastatic nodules. Under the latter conditions, we also have found the parietal pleura studded with tumor masses, some of which were large and fungating In 2 cases, the liver presented numerous metastases, mainly in the form of nodules, varying from a few millimeters to somewhat more than a centimeter in diameter In one case or another metastases were noted in one or more of the following organs heart, spleen, kidneys, pancreas, and thyroid. Finally it should be noted that the lymph nodes, by and large, tended to be free of neoplastic tissue although in one case some of the paravertebral and pelvic lymph nodes showed microscopically some nests of tumor cells in the peripheral sinuses as extensions of the neoplasm from the underlying vertebrae The striking lack of involvement of the lymph nodes is additional evidence against the possibility that an occult primary carcinoma or neuroblastoma was present.

As already indicated, one can expect to find at autopsy that a *major part of* the skeleton, in addition to the bone containing the presenting lesion, is affected, and much more extensively than one would have suspected from the ante-mortem roentgenograms. The question which cannot be answered definitely is whether the wide dissemination through the bones represents metastatic spread of the neoplasm or rather development independently in multiple sites. At any rate, the calvarium is likely to show the neoplasm permeating the diploic spaces, and, in addition, areas in which neoplastic tissue has eroded or completely destroyed the tables. In the latter case, the calvarium will show actual *defects*, frequently several centimeters in diameter filled with cellular gray white or green-yellow neoplastic tissue which may elevate or even penetrate the regional calvarial coverings. The marrow spaces of the ribs and sternum, too, are likely to be filled with neoplasm, and thinning and erosion of the cortex may be associated with focal masses of neoplastic tissue beneath the periosteum. In both cases in which we did autopsies, large sections of the vertebral column were removed, and here too we found the

marrow spaces of the bodies, arches, and spinous processes extensively infiltrated. In one case in particular practically every dorsal and lumbar vertebral body showed areas in which the neoplasm in the marrow spaces and the supporting spongy bone appeared yellowish in consequence of necrosis. Where there was no necrosis, the neoplastic tissue was grayish, soft, and obviously cellular In many places the neoplastic tissue was extending through the bodies beneath the anterior vertebral ligament. From the third dorsal segment to the first lumbar segment, the new growth had also extended beneath the dura, narrowed the spinal space and cuffed and compressed a large section of the spinal cord, with resultant degeneration of the latter

Microscopic Findings

Although Ewing's sarcoma does have a characteristic cytologic pattern, secondary changes may obscure it or make it difficult to demonstrate in an individual specimen taken for biopsy even if this has been obtained by surgical incision. Thus, a given specimen may show large fields in which the appearance of the individual tumor cells has been altered by degeneration and necrosis, areas in which the neoplastic tissue as a whole has been modified by hemorrhage and reparative reaction to it, and even areas in which reactive inflammatory changes dominate the picture. It is because such secondary changes are not relegated to the background that the reputation of Ewing's sarcoma for variability and inconstancy of its cytologic pattern in biopsy specimens from case to case has developed and persists.

However secondary changes in the neoplastic tissue do not present the only difficulty with which one is confronted in attempting to make a diagnosis of Ewing's tumor on the basis of a biopsy specimen. The diagnosis "Ewing's sarcoma" often has become a mere refuge when one is confronted by a puzzling malignant tumor in a bone, and is likely to be applied rather loosely and by default of a better opinion unless one's anatomic concept of Ewing's sarcoma is a definite one.

The characteristic cytology of Ewing's sarcoma is manifested in the presence of fields of tumor cells which lack clearly delimited cell boundaries, and whose nuclei are crowded together and are of fairly uniform appearance. These nuclei are round or ovoid are about twice as great in diameter (or in the case of the ovoid ones, perhaps three times as great in their longer axis) as the nucleus of a lymphocyte, and have finely divided or powdery chromatin and often one or more nucleoli. As a rule the individual nuclei appear enmeshed in and are slightly separated by a loose, more or less vacuolated cytoplasmic fabric. In some fields, however they may be found crowded together (perhaps to such an extent that many of them are even pressed into an oval shape) and in such fields there is but little cytoplasm between them. It should also be noted that in the fields presenting the general cytologic picture just described, vascularity is usually not a prominent feature (Figs. 135 and 136)

Cellular areas showing the characteristic cytology just described have to be searched for in a biopsy specimen from the presenting bone lesion, since the neoplastic tissue may have undergone extensive degeneration and necrosis. Degeneration causes the nuclei to appear small and pyknotic, and such nuclei are likely to

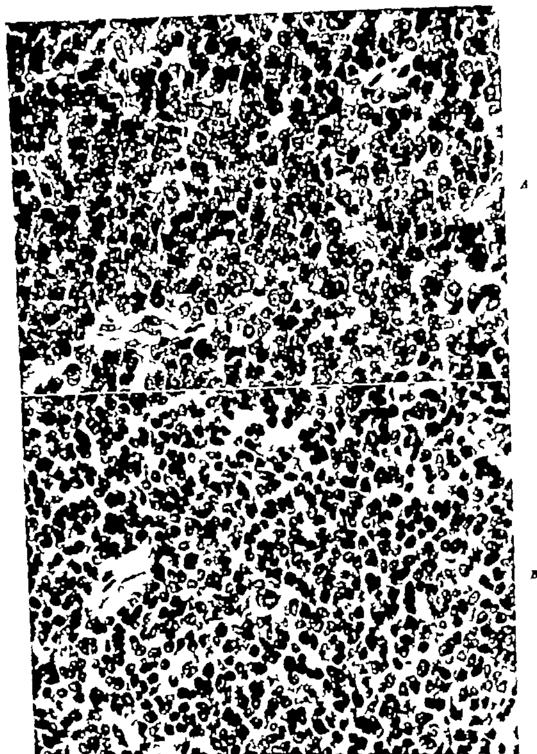


Fig 135—*A* and *B* Photomicrographs of two representative instances of Ewing's sarcoma, illustrating its basic cytologic pattern, unmodified by hemorrhage or by degeneration and necrosis. The tumor cells are closely packed and uniform in appearance (as compared with reticulum-cell sarcoma) (see Fig 161) and have an indistinct cytoplasmic outline and scattered chromatin within the nuclei, which often gives them a relatively dark or smoky appearance. (×475.)

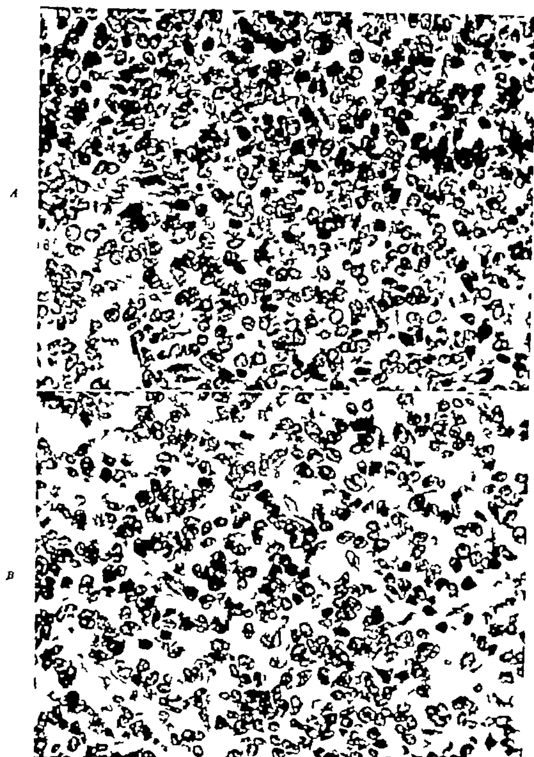


Fig 186.—*A* and *B* Photomicrographs of two additional Ewing tumors to show variation in pattern (×475)

be surrounded by a narrow zone of cytoplasm with a delimiting cell border It apparently is such distorted cells, commonly observed in biopsy specimens, that Ewing described as the representative cell type namely a small polyhedral cell with pale cytoplasm, a small hyperchromatic nucleus, and a well-defined cell border Intermingled with fields in which the tumor cells are undergoing degeneration there are usually areas in which the cells have also undergone necrosis. Such areas may in places, be heavily infiltrated by polymorphonuclear leukocytes. Hence, if only a limited fragment of tissue is examined and sufficient care is not taken, this picture may be misinterpreted as indicating an infectious process rather than a tumor

Extensive hemorrhage into fields of neoplastic tissue comes to be associated with the ingrowth of many blood vessels. If the neoplastic tissue in these areas is not necrotic, one will note that many of these vessels are collared by tumor cells. However, the vessel spaces are not lined by tumor cells and between the latter and the lining cells there is tissue representing the wall of the vascular space. Thus while it is true that in such fields one does see tumor cells about capillary spaces or around larger vascular spaces in so-called "perithelial" arrangement, one does not see this orientation of tumor cells to any pronounced extent except in connection with hemorrhage. It is on this account that no distinctive cytologic significance should be ascribed to such findings. Similar perivascular orientation of tumor cells is observed in connection with sarcomas of other kinds in which focal areas have undergone extensive hemorrhage.

We will consider next the question of the presence of rosette (or pseudorosette) formation. In connection with an occasional Ewing's sarcoma, some authors have reported and illustrated formations in which cells are arranged circularly (although not around a vessel) in so-called rosette formation However in such illustrations it can be seen that the centers of these formations represent degenerated cells with shadows which are still perceptible, rather than fibrillar or granular cores as in neuroblastoma. The "pseudorosettes" illustrated by Gharpure in his case of Ewing's sarcoma clearly show that the core about which the viable tumor cells are circularly disposed represents a mass of necrotic tumor cells, the outlines of which are still plainly visible. Also the "rosettes" illustrated in the case presented by Foote and Anderson seem likewise to appear in tissue fields where cells are undergoing necrosis.

In regard to the reticulin fibrils in Ewing's sarcoma it appears that these are not a consistent or prominent feature of the histologic picture There is considerable variability in regard to these fibrils, from lesion to lesion and even from part to part of the same tumor section. Some lesions, in part or throughout, present merely a few scattered argyrophil fibrils in an entire low-power field. Other lesions show more numerous fibrils, but these are irregularly distributed and are noted between smaller and larger groups of tumor cells. In no instance did we regularly observe large fields of tissue showing a lattice or meshwork of reticulin fibrils outlining not merely cell groups, but the individual tumor cells as well Altogether it would appear that there is no characteristic histologic pattern for Ewing's tumor in so far as these argyrophil fibrils are concerned.

Differentiation From Neuroblastoma With Skeletal Metastases

That sympathetic neuroblastoma (sympathicoblastoma) commonly metastasizes to bones has been known for a long time. Hutchison, and Tileston and Wolbach have pointed out that a malignant adrenal tumor is often the primary lesion in infants and children who clinically present tumorous involvement of cranial bones, proptosis and enlargement of the preauricular and other regional lymph nodes. From the cases reported by these authors, and from those which they collected from the literature (cases now assignable to adrenal neuroblastoma) it is evident that metastases to bones other than those of the skull are often found, and that metastases to the liver kidneys, and lymph nodes as well are also rather common.

Further observations have clearly indicated that, although the adrenal medulla is the most common site of origin for neuroblastomas, it is by no means the only one. Cases have been reported in which they arose from sympathetic nervous tissue elsewhere in the body notably from the sympathetic chains, but sometimes even from the sympathetic tissue of organs. While infants and young children are the most common subjects, occasional instances have been reported in which sympathetic neuroblastomas developed in adults. Also, it has become clear that in so far as the skeleton is concerned, the clinically presenting, destructive bone lesion (if there is one) may be in a long bone or some bone other than the skull.

In respect to cytology Tileston and Wolbach stressed the diagnostic significance of the finding of tumor cells arranged in rosettes. It was Wright who pointed out that these tumors take their origin from the pluripotential cells of the sympathetic nervous system, and that the rosettes are ball like aggregations of tumor cells enclosing a small central meshwork of filamentous neurofibrils, some of which can be seen to constitute processes of the cells making up the periphery of the rosette. In addition, he pointed out that, aside from rosettes, one may be able to find masses of tumor cells interspersed with and penetrated by fibrils running parallel in bundles. However the demonstration of neurofibrils, either in parallel bundles or as a meshwork in the center of the rosettes may be difficult. In such instances, few fibrils may have been laid down or as a result of degeneration or post mortem change, the fibrils may have become transformed into hyaline or granular material and be difficult to demonstrate. This is especially true of the fibrils of the rosettes. Under such circumstances, whatever rosettes are present appear as formations in which several rows of cells surround a finely granular eosin-staining mass without a central lumen.

In any particular case, rosettes may be fairly numerous in both the primary growth and the metastases, conspicuous in the primary growth and sparse in the metastases or difficult to find in either As to the type cell of the tumor there are differences from lesion to lesion, depending on the predominant level of maturation. In the most primitive type, this cell maintains the lymphocytoid character of the parent stem cell. It is usually a small round cell (strongly resembling a small lymphocyte) with a dense hyperchromatic nucleus practically filling the entire cell so that there is little cytoplasm. Some of the cells, although maintaining this

general character may be oval while others, especially at the periphery of the rosettes, may be piriform. In more differentiated sympathetic neuroblastomas the cells, although mainly round are distinctly larger than those just described and may have vesicular nuclei and a clear ring of cytoplasm about the nucleus, and often some cytoplasmic processes. In still further matured neuroblastomas, some tumor fields may even show sympathetic ganglion cells.

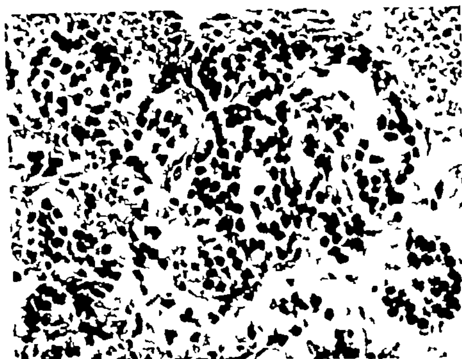
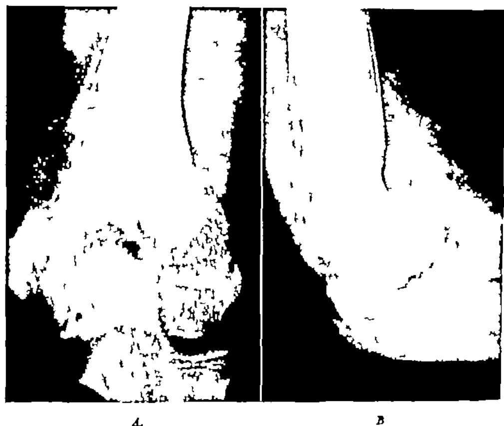


Fig. 157.—Photomicrograph of a neuroblastoma (of an adrenal) for comparison with Figs. 155 and 156. The ghost outlines in the background are those of red blood cells. (×475.)

With this background, we are in a better position to understand Willis point of view concerning neuroblastoma in relation to Ewing's sarcoma. Prior to the publication of the relevant articles by Willis and by Colville and Willis, it seems not to have been adequately stressed that care must be taken to exclude the possibility that one may actually be dealing with a sympathetic neuroblastoma metastatic to the skeleton in cases which apparently represent Ewing's sarcoma of bone. In both cases cited there was a presenting bone tumor which had the usually accepted clinical and roentgenographic characteristics of Ewing's sarcoma. The clinical course, and in particular the susceptibility of the tumor to radiation therapy seemed further to support this diagnosis. However in both cases it was revealed at autopsy that the presenting bone tumor (in a femur) represented a metastasis from a neuroblastoma, primary in an adrenal in one instance and in the left lumbar sympathetic chain in the other In each instance rosettes were found only in the primary growth and not in the biopsy specimens.

On the basis of these experiences, Willis expressed great wariness about accepting a diagnosis of Ewing's sarcoma made on clinical and roentgenographic grounds alone. He cast doubt also upon the reliability of biopsy in this connection, and analyzed, largely to reject them, the findings in the relatively few cases published prior to 1940 which had been interpreted as Ewing's sarcoma proved by autopsy. His paper of 1940 bears careful reading for its astute evaluation of the reported autopsied cases of Ewing's sarcoma, even if it does appear that in some instances he has perhaps been overcritical.



A. *B.*

Fig. 138.—*A* and *B*. Roentgenograms of a lesion in the lower humerus of a 10 year old child, which clinically presented a difficult problem in differentiation between osteomyelitis and Ewing's sarcoma. At the time of biopsy the surgeon encountered soft, whitish material which he thought to be pus. However, sections of the bone fragments from the medullary cavity showed small foci of Ewing's tumor within the marrow.

There can be no doubt that Willis was correct in maintaining that a presenting bone lesion which is in fact a metastasis of neuroblastoma may not be recognized as such on the basis of biopsy, and the following case from our own material illustrates this. The patient was a boy 3 years of age, who was admitted because of pain in the left hip region and limp of 3 months' duration. Roentgenograms revealed a rarefying lesion in the neck of the left femur, resorptive destruction of the cortex in this area, and some periosteal new bone apposition on the adjacent portion of the femoral shaft. On the assumption that the lesion was a low-grade

osteomyelitis, it was curetted, but this assumption could scarcely have been made if the child had been studied thoroughly before surgical intervention, for on admission, the child already presented a dilated left pupil and evidences of general lymphadenopathy especially prominent in the left cervical region. The tissue sections from the material curetted from the neck of the femur showed a malignant tumor. The tumor cells were supported in a connective tissue stroma which was

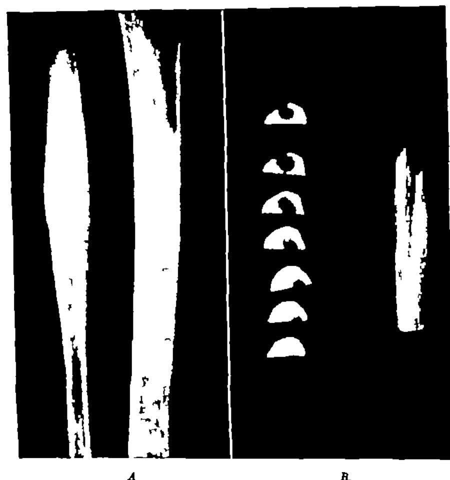


Fig. 139.—*A*. Roentgenograms of a fusiform expanded lesion in the shaft of a fibula which was thought clinically to represent a Ewing's sarcoma. The surgical procedure was excision biopsy of the involved segment. *B*. Roentgenograms of serial transverse slices of one half of the resected thickened fibula showing that the oblique rarefied tract illustrated in *A* reflects the presence of a chronic bone abscess. The periosteal new bone has developed as a reaction to extension of this abscess to the outer surface of the cortex.

loose in some places, rather collagenous in others, and tended to demarcate smaller or larger groups of the cells. The predominating type of cell was rather large and round lacking a clear-cut cytoplasmic outline and having a large, pale, stippled nucleus. Although some smaller cells with dark hyperchromatic nuclei were present, a number of tumor giant cells, some of which had two or more nuclei, were also seen. The cytologic picture was not that which one associates with Ewing's sarcoma

nor on the other hand, was it even vaguely suggestive of neuroblastoma. However that the femoral lesion was actually a metastatic neuroblastoma was clearly established by histologic examination of several enlarged lymph nodes from the left cervical region, which showed unmistakably the rosettes and other cytologic features of sympathetic neuroblastoma. Unfortunately we could not determine the site of origin for the neuroblastoma in this case, since there was no autopsy for the child died at home about 1 year after the onset of the complaints.

This case of sympathicoblastoma was peculiarly difficult to diagnose, and makes us sympathetic to Willis' contention that only carefully executed autopsies can prove or exclude neuroblastoma or completely justify a diagnosis of Ewing's sarcoma. However that a large proportion of cases of sympathetic neuroblastoma have certain distinctive clinical and roentgenographic features which are useful in differentiating them from Ewing's sarcoma can be gathered from the mass of material on which Wyatt and Farber have reported. As to our own 13 cases in which the diagnosis of Ewing's sarcoma was based on biopsy findings, it can be said that, in view of the uniformity of the cell type in these cases and its consistent resemblance to the cell type observed in the 4 autopsied cases, we feel reasonably confident in assuming that we could not have been dealing in all 13 cases with metastases from neuroblastomas. This assumption seems all the more justified if one bears in mind these pertinent considerations None of the many tissue sections cut in these 13 cases showed the rosettes classic for neuroblastoma If these 13 lesions represented metastases from neuroblastomas, the primary tumor in all these cases would have had to be silent and the cells in all the lesions would have had to be matured to, and only to, the sympathoblast level all but one of these 13 patients was over 8 years of age, whereas the great majority of cases of neuroblastoma are seen in children under this age.

Differentiation From Carcinoma and Other Malignant Tumors With Skeletal Involvement

The problem of the differential diagnosis of Ewing's sarcoma does not end with sympathicoblastoma, but may be raised also by metastatic carcinoma. That a solitary destructive bone lesion which is proved by biopsy to represent a metastasis may be the first clinical indication that the patient is suffering from carcinoma hardly needs to be stated. It is also common to find that, while the primary neoplasm is silent, the histologic picture of the neoplastic tissue in the biopsy specimen affords a clue to the site of the primary growth. On the other hand, there is often insufficient cytologic differentiation to suggest the site of the primary lesion. Diagnostic difficulties arise particularly in those cases in which the primary growth is silent and in which the neoplastic tissue in the metastatic focus is so undifferentiated as to present a more or less uniform pattern of round cells. Although this problem does sometimes arise in connection with biopsy diagnosis or even in connection with the evaluation of the autopsy findings in a suspected case of Ewing's sarcoma, it does not constitute a frequent or serious difficulty in the hands of an experienced pathologist. Still Hirsch and Ryerson have pointed out that bronchial

carcinomas (particularly small ones composed of undifferentiated cells) may metastasize widely to the bones before being recognizable in the lung and thus raise problems of differential diagnosis from Ewing's sarcoma. This point of view has also been stressed by Sternberg who cited a case in which a skeletal metastasis was regarded as Ewing's sarcoma although he himself held that involvement of bone was secondary to an undifferentiated small-celled carcinoma of the breast.

Finally it may be relevant to point out that occasionally in the course of evaluation of a biopsy specimen, one may have to make a differential diagnosis between Ewing's sarcoma on the one hand and Hodgkin's disease or lymphosarcoma on the other However the latter conditions are so rarely primary in bones that one is not often confronted by this problem as a practical difficulty and when they are not primary there, the general clinical picture in which involvement of lymph nodes occupies the foreground helps to clarify the problem.

Treatment and Prognosis

The problem of giving counsel in regard to treatment of a tumor diagnosed as Ewing's sarcoma from a satisfactory biopsy specimen presents a disheartening dilemma. It has been demonstrated repeatedly that while adequate x ray therapy may bring about remarkable amelioration of complaints referable to the presenting tumor site, such patients generally die of "improvement," usually within the ensuing 2 or 3 years, and manifest at autopsy widespread skeletal involvement and also visceral extension, notably to the lungs. On the other hand, if one advocates ablation or radical surgical resection (for a tumor in an accessible site) one can offer the patient or his family but meager hope for cure, or even survival for as long as 5 years. In the 17 cases covered by this survey, there was not a single cure, even in those cases in which surgery was resorted to promptly after the diagnosis was established, and all but 3 patients were dead within 3 years of the onset of symptoms. Otherwise, I have personal knowledge of only a single cure, in a patient who is known to be alive and well 20 years after amputation of a lower limb for a tumor of the fibula, diagnosed as Ewing's sarcoma. (I have reviewed the biopsy slide and am willing to accept the tumor in question as a Ewing's tumor)

In the survey conducted by Coley and his associates, it is reported that only 3 out of 73 patients (4 per cent) survived 5 years or more. One of these patients, stated to be well 12 years after treatment, received rather heavy x ray irradiation for a tumor in the upper shaft of a humerus, without supplementary ablation. It is relevant to note further that as of 1935 the Registry of Bone Sarcoma reported that 10 patients of some 126 registered cases of Ewing's sarcoma, all of them surgically treated, had survived from 5 to 21 years following treatment. While these results appear a little more encouraging one must bear in *mind* that the pathologic diagnoses recorded represent the opinions of many observers, not all of whom were fully conversant with the subtle problems in differential diagnosis. As such, these impressions are subject to verification before they can be accepted at their face value. It is not unlikely for example, that at least some of the tumors in question may have represented primary reticulum-cell sarcomas still limited to a single bone marrow focus. By the same token, one must be guarded

in the matter of accepting the follow-up data cited by Geschickter and Copeland to the effect that of 127 patients treated as having Ewing's sarcoma, there were as many as 13 five year survivals (approximately 10 per cent) The same reservation applies also to the published data of Meyerding and Valls, who have reported a 5 year survival rate of 21 per cent. This conclusion is so out of line with the experience of other observers that it may not be amiss to remark that before one attempts to grade a neoplasm, one should be reasonably certain of its identity



Fig 140.—*A* Roentgenogram of a relatively early lesion of Ewing's sarcoma in the lower fibula of a 19-year-old girl, showing slight but definite mottled rarefaction of the spongiosa and cortex, along with rather subtle periosteal reaction (more clearly seen in the original). Amputation was resorted to without delay in spite of which pulmonary metastasis appeared about a year later as shown in *B*.

These more favorable reports notwithstanding, I have the distinct impression that Ewing's sarcoma carries a grave prognosis even under favorable auspices, and that, irrespective of the type of treatment employed, the expectancy for survival beyond a few years is rather slim. That there are occasional cures, however seems equally clear from the available evidence. It has always seemed to me that Ewing's sarcoma must be regarded essentially as a multicentric tumor tending sooner or

later to spread over the skeleton, but that there might well be very occasional instances in which the neoplastic process is more limited or even confined to a single bone. This might account for the few cures which have been observed.

Taking cognizance of the foregoing considerations, I am now inclined to recommend irradiation rather than radical surgery. Irradiation may be expected

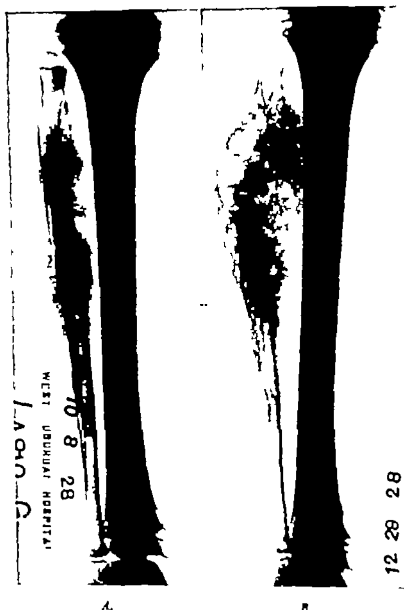


Fig. 141.—A and B. Roentgenograms of a Ewing's sarcoma of a fibula showing rapid progression of the neoplasm over a period of less than 3 months. Amputation was performed, and the patient is known to be alive and well, over 20 years later. I have reviewed the biopsy slide and am satisfied that the neoplasm was a Ewing's tumor and not a reticulum-cell sarcoma. This case is significant in that it represents one of the very few cures in Ewing's sarcoma of which the writer has personal knowledge.

to destroy the presenting tumor (if it has not already grown to bulky size) and to ameliorate the patient's complaints. It will not prevent the appearance of tumor foci elsewhere in the skeleton or eventual pulmonary metastasis, any more than surgery will. Since, with few exceptions, the anticipated survival period before dissemination is only a few years, five at the outset, there seems to be little point in subjecting the patient (and the family) to the trauma of the loss of a limb.

Summary and Conclusions

This study (based on 17 cases in 4 of which autopsies were done and supplemented by numerous subsequent observations) supports the existence, among the primary malignant tumors appearing in bones, of a tumor entity to which, because of Ewing's pioneer effort to single it out, the name of Ewing's sarcoma should be applied. Beyond the fact that it is a specific malignant tumor primary in bone and that its cells show no osteogenic potentialities, there is still much to be learned in respect to its histogenesis. Study of the cytologic patterns in our material yields no support for Ewing's contention that the neoplastic cells are derived from capillary or vascular (or perivascular) endothelium. It is true that tumor areas which have become heavily invaded by blood vessels, especially in the wake of hemorrhage, often show tumor cells about capillary spaces or around larger vascular spaces in a so-called "perithelial arrangement," but perivascular orientation of the tumor cells is not a characteristic cytologic feature of this neoplasm. Also, when, in an occasional lesion, one finds formations in which cells show a ringlike arrangement (though not around a vessel) these formations can be seen to have resulted from degeneration of centrally located cells, the shadows of which are still perceptible. Such formations really have nothing in common with the rosette or pseudorosette formations of neuroblastoma.

We incline toward the view that the tumor cells of Ewing's sarcoma are derived from the supporting framework of the bone marrow a framework which can be regarded as a mesenchymal or primitive form of connective tissue. Ewing described the type cell of the lesion as a small polyhedral cell with pale cytoplasm, a small, hyperchromatic nucleus, and a well-defined cell border However as revealed in viable, well fixed and well-stained neoplastic tissue, the type cell is actually found to have an ill-defined cell border little cytoplasm, and a fairly large, round or oval nucleus showing scattered chromatin. Nevertheless, to make a diagnosis of Ewing's sarcoma from a biopsy specimen, even if the latter is obtained by surgical incision is sometimes difficult because of secondary changes which the neoplastic tissue has undergone. Cell areas showing the characteristic structure are sometimes to be found only after many sections have been made and examined.

A diagnosis of Ewing's sarcoma on the basis of biopsy should not be made without giving consideration to the possibility that one may be dealing with a sympathetic neuroblastoma or anaplastic carcinoma metastatic to the affected bone. Such alternative possibilities as primary reticulum-cell sarcoma of bone, Hodgkin's disease, malignant lymphoma, and even myeloma must be eliminated. If in a patient suspected of having Ewing's sarcoma, enlarged lymph nodes are

palpable (regionally to the affected bone, or elsewhere) these too should be examined anatomically in consideration of alternative possibilities, since lymph nodes are not commonly involved in Ewing's sarcoma, at least in an early stage.

On the clinical side, in our cases of Ewing's sarcoma we found that the great majority of the patients were in the second decade of life. The clinical histories did not show trauma to be an instigating factor In the majority of our cases, the presenting lesion was in a bone of the trunk. We found no evidence favoring the idea that the presenting bone lesion shows a characteristic, if not typical roentgenographic picture of high diagnostic value.

Ewing's sarcoma has a most doleful prognosis. Relatively few patients survive as long as 5 years after treatment, whether this be surgery or irradiation and only a very occasional one beyond this. Fever secondary anemia, and an increased sedimentation rate of the blood in a patient with Ewing's sarcoma are evidences that the course will be a fulminating one, ending in death within a few months. Radiation therapy alone, while often having a remarkable palliative local effect for some time, will not prevent the appearance of tumor elsewhere in the skeleton or eventual pulmonary metastasis, any more than amputation will. In these circumstances I am now inclined to recommend irradiation since there seems to be little point to subjecting the patient (and the family) to the trauma of the loss of a limb

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only infrequently that gross myelomatous foci are found in the viscera and other extraskeletal parts. Nevertheless, even in the absence of gross infiltrations, microscopic examination sometimes reveals the presence of smaller or larger numbers of myeloma cells within the spleen, the liver, or the lymph nodes, and occasionally in other organs as well. Also, in some cases myeloma cells invade the blood stream. Ordinarily, under these circumstances, relatively few myeloma cells are found in



Fig 142.—Roentgenograms showing the skeletal changes observed at autopsy in a far-advanced case of multiple myeloma. *A* In the shaft of the femur. *B* In the vertebral column and in the sternum, the body of which shows a previous pathologic fracture. *C* In the ribs, which are reduced to thin shells honeycombed by myeloma.

the blood smears. However in an occasional case they may be so numerous as to create a leukemic blood picture (so-called plasma-cell leukemia)

In 1947 in collaboration with Jaffe, I had occasion to survey the hospital's material on multiple myeloma comprising some 35 cases, 18 of which came to autopsy The discussion that follows is based largely upon inferences gleaned from that survey and from numerous subsequent observations, as well, though taking full cognizance also of the rather voluminous pertinent literature. In all but 3 of these



Fig 145—Roentgenograms of another far advanced case of multiple myeloma. *A* Compression fracture of vertebra associated with extreme osteoporosis. *B* Pathologic fracture of neck of femur as well as striking osteoporosis and myelomatous transformation of innominate bone and upper femur

35 cases the diagnosis of myeloma was confirmed by examination of tissue. In the 3 excepted cases although Bence Jones proteinuria was found in only 1 the diagnosis seemed fairly certain from the fact that hyperglobulinemia or hypercalcemia or both were in association with roentgenographic skeletal changes consistent with multiple myeloma. In the great majority of our cases the roentgenographic examination was not limited to the skeletal region giving clinical difficulties but, indeed.

covered a substantial part of the skeleton, so that the full extent and distribution of the tumor process was mirrored. In more than half the cases, particularly in those observed in recent years, chemical estimations of serum albumin and globulin and of serum calcium were made. In all but a few of the cases the urine was examined for Bence Jones protein, often repeatedly. As noted, 18 of the 35 cases came to autopsy. The examination of these 18 included a detailed study of the



Fig. 144.—Roentgenograms from additional cases of multiple myeloma coming to autopsy. *A*, Femur showing a circumscribed lytic defect where a tumor focus has encroached upon and eroded the cortex. *B*, Humerus showing moth-eaten and also more discrete areas of rarefaction. *C*, Extensively involved ribs showing thinned cortices, honeycombed rarefaction, and pathologic fractures.

skeleton. Specifically, much of the vertebral column, the sternum, many of the ribs, parts or all of the pelvic bones and, in many instances, some of the long bones and the calvarium were removed and cut open. Furthermore, in many instances the sectioned bones were then roentgenographed, and in all instances tissue was removed from many representative areas and studied microscopically.

Clinical Considerations

Age and Sex Incidence.—Fully three fourths of the patients were between 40 and 60 years of age. This finding is in accord with the generally accepted view that multiple myeloma shows a predilection for persons who are in later middle life. The incidence of the disease appears to fall off sharply in persons who are past 60 years. As to its incidence in persons less than 40 years of age as noted it is by no means unusual in those who are in the 30's but is rather rare in those who are less than 30 years of age. Only one of our patients was below this age, the one in question being a 17 year-old boy who presented the first manifestations of the disease at the age of 13 years. A few unequivocal instances of multiple myeloma occurring in adolescents or children have also been reported. Some others, less convincing in the literature may actually be instances of Schüller Christian disease, stem-cell leukemia, Ewing's sarcoma, or neuroblastoma that has metastasized to the skeleton.

As noted, our data indicate that multiple myeloma may be slightly more prevalent in males than in females but do not support the often repeated statement that the condition is at least twice as frequent in males

Clinical Complaints.—Evaluation of the clinical records of our cases showed that the major difficulties (occurring singly or in combination) which brought the patients to the hospital were, in the order of decreasing frequency (1) pain, especially of the back and the thorax, (2) substantial loss of weight, (3) pathologic fracture of some bone, and (4) a palpable tumor appearing in relation to a superficial flat bone. It should be pointed out, however that patients seeking admission to our hospital tended to do so mainly because of complaints directly referable to skeletal alterations rather than because of anemia, abnormal bleeding neurologic symptoms, or findings suggesting nephritis.

The pain occurring in the back and the thorax was often vague and generalized, and accompanied by a feeling of weakness. However in the presence of compressed or collapsed vertebral bodies it had a more localized, persistent, and disabling character and was frequently associated with some manifestations of compression of the spinal cord or at least of issuing nerve roots. The loss of weight amounted to thirty pounds or even more in some cases. As the disease progressed, there was a tendency even in those who showed no appreciable loss of weight on admission, toward increasing debilitation and terminal emaciation. Pathologic fracture as expressed in compression collapse of one or more vertebral bodies was not uncommon but in some cases a femur or a humerus, for instance, presented a pathologic fracture extending through an area of exuberant myelomatous involvement. If one or more tumor masses are palpable on the skeleton, they are most likely to be found in relation to a clavicle or to one or several ribs. However a tumor may sometimes be palpable in relation to such superficial bone sites as the calvarium or the facial bones, the sternum, a scapula, or an innominate bone.

Presenting Skeletal Lesions.—There are some cases of multiple myeloma in which the patients complain of rather generalized bone pain without specific localization, in spite of widespread skeletal involvement. Usually however it is

difficulty with some particular bone or skeletal region that first directs attention to the presence of the disease. The involved site most often responsible for difficulties in those whose initial skeletal complaints were localized was the vertebral column. Indeed, in approximately one half of these patients the difficulties were referable to the spine. The lumbar region was most often affected, next the dorsal, and least often the cervical region. Patients having complaints referable to the vertebral column often showed roentgenographic evidence of compression or collapse of one or more vertebral bodies on admission to the hospital, and a number of them presented signs of resulting compression of the cord as well. It seems worth mentioning that, with involvement of the lumbar region of the spine, disability and sciatic pain were common complaints even in the absence of compressed or collapsed vertebral bodies.

The long bones, particularly the femur represented another clinically important site of localization. Specifically, there were 5 patients, each of whom presented in a femur a strikingly large focus of myeloma that rendered the area easily susceptible to pathologic fracture. This large focus of destruction was found sometimes in the midshaft and sometimes at the end of the shaft. Roentgenographically, the femoral lesions were regularly misinterpreted as representing something other than multiple myeloma until their true nature was established by biopsy Large, destructive lesions comparable to those observed in femurs were also observed occasionally in humeri.

When it occurs in a superficially located bone, the presenting lesion is also likely to be clinically palpable Thus, not infrequently such a tumor can be felt on a rib or a clavicle. Actually however even a bone of a foot or a hand may sometimes be the site of the presenting lesion.

Clinical Course and Prognosis.—In many cases the disease pursues an insidious course in the beginning the patient complaining merely of some weakness, loss of weight, or vague pain in the back or the chest. Sometimes, a fracture of some bone (commonly a rib or a limb bone) weakened by an exuberant focus of tumor within it is the first major difficulty In other instances the disease may be ushered in dramatically by sudden onset of severe root pain or even paraplegia resulting from compression or collapse of one or more vertebral bodies. Taking our cases altogether we find that the duration of symptoms prior to hospitalization ranged from as short a time as a few weeks to as long as 2 years, the average duration being about 9 months.

Whatever the initial complaints that bring the patients to the hospital, the progress of skeletal involvement thereafter as judged by successive roentgenograms, is rather variable and frequently unpredictable. The patients who present a far advanced stage of the disease when first observed usually (though not invariably) survive no more than some weeks or months. As for those with still limited involvement roentgenographically in some one observes tremendous progression within just a few months, while in others one gains the impression that the neoplasm progresses relatively slowly or remains static for months or even a number of years before entering its terminal phase. This variability of tempo is not explain-

able on a cytologic basis alone. The average period of survival following the onset of symptoms was about 2 years in our cases, which is in accord with the general impression, but there are striking deviations from this average. Two patients in whom transverse myelitis developed succumbed within 1 and 3 months, respectively although it is true that neither of them received the possible benefit of laminectomy for decompression. On the other hand, we did an autopsy in a case in which the history of the disease dated back over 9 years, and another patient (presenting tumor in an ilium initially) was still alive and comparatively well after 10 years. While these instances are exceptional, it is well known that the clinical course of multiple myeloma may occasionally be protracted and characterized by long remissions, which are frequently attributed to roentgen treatment but which may be spontaneous. Cases in point have been reported by Gross and Vaughn, Kirsch, Batts, and Davison and Balser. The latter cited an extraordinary case which came to autopsy 16 years after the onset of symptoms. It is true also that patients in whom the tumor is apparently localized in some one bone in the beginning not infrequently go on for a number of years before the myeloma becomes disseminated over the skeleton.

In most cases, as the disease progresses there is a tendency toward demineralization and devastation of the skeleton, associated with increasing anemia and cachexia, provided the clinical course is not cut short, as it frequently is, by such complications as intercurrent infection (especially pneumonia in bedridden patients) concomitant cancer of some other kind, cardiac failure renal insufficiency ascending infection of the urinary tract, or amyloidosis.

Problems of Diagnosis

There are numerous cues to the diagnosis of multiple myeloma coming from many quarters — clinical, roentgenographic, hematologic, biochemical — and the recognition of the condition prior to biopsy or post-mortem examination frequently requires their fullest utilization. It is true that the diagnosis of multiple myeloma will be fairly obvious if many bones, including the calvarium, are veritably *riddled* by osteolytic defects (the picture usually stressed in the texts) and if in addition, Bence Jones proteinuria is discovered. Unfortunately this skeletal picture represents the exception rather than the rule, in our experience at least, and Bence Jones proteinuria is as likely to be absent as present. One often observes merely some vaguely defined rarefactions in some of the bones or a single exuberant tumor in a single bone without obvious involvement of the skeleton generally and sometimes (when myelomatous infiltration of the bone marrow is diffuse) skeletal changes may not be apparent at all roentgenographically in spite of complaints referable to the skeleton. In such equivocal or initially obscure cases the lead may come from the discovery of anemia, the presence of myeloma cells in blood smears, hypercalcemia, hyperproteinemia (and certain peculiar hematologic manifestations resulting from increase of serum globulins) evidences of renal damage of a peculiar type, or even from the finding of unusual tumorlike amyloid deposits. It must be

recognized, however that these pertinent findings are not all present in every case or necessarily present in the early stages of the evolution of any given case, nor are they necessarily pathognomonic in themselves. It is only by utilizing all the *logical approaches that one is likely to arrive at a combination* of significant findings constituting probable or conclusive evidence of the presence of multiple myeloma.

For anatomic confirmation, puncture of the sternal marrow should be freely employed. A high degree of reliability is claimed for this procedure, though there are undoubtedly cases of multiple myeloma in which sternal marrow spreads fail to yield significant information. Biopsy of some obviously affected and readily accessible bone will resolve any possible doubt as to the diagnosis, since the histologic recognition of a myeloma entails no difficult problems in differential diagnosis as a rule.

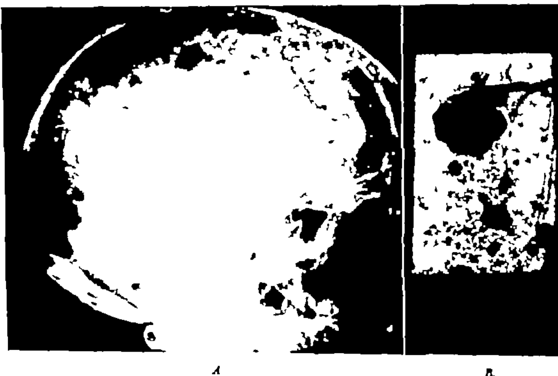
Skeletal Alterations and Their Roentgenologic Reflection

No single description can do justice to the gross appearance of the bones in all cases of multiple myeloma coming to autopsy At one extreme there is the occasional case in which the bones appear normal as to surface and contour and those removed do not even offer any striking lack of resistance when being cut open. On inspection of the cut surfaces of these bones, one finds that the spongy trabeculae are still numerous and that the cortices are not significantly thinned. However the marrow is modified and replaced more or less diffusely by rather whitish tissue which, on histologic examination, is proved to be myeloma tissue. In conformity with these findings, the skeletal roentgenograms taken during life in such a case may show at most some diffuse porosity of the bones. They certainly show nothing even remotely suggestive of the roentgenographic picture one has been taught to regard as representative of multiple myeloma. This was the skeletal status in a case of atypical amyloidosis and myeloma which we studied. It re-emphasizes the fact that in every case of atypical amyloidosis, despite the lack of evidence of multiple myeloma in the clinical roentgenograms, bones must be opened and their marrow examined histologically to establish or rule out the presence of myeloma.

In another occasional case while the bones show smooth and undistended contours they cut with abnormal ease. When cut, such bones show thinning of the cortices from the medullary side as well as great reduction of the spongy trabeculae. This is the result of encroachment on the osseous tissue by a whitish-gray tissue which has substantially replaced the marrow and which stands out in some places as discrete foci of tumor The clinical roentgenograms of the bones in such a case hardly suggest the conventional idea of the roentgenographic picture of multiple myeloma but do reflect the tumor encroachment on the osseous tissue by showing vague mottled or vacuolated rarefactions and thinned cortices.

In many cases, however the cortex becomes gravely weakened or even destroyed by the tumor tissue in one or several places of one or even of many bones Thus, there is a bulge in the contour of the bone at such a site, and the

tumor tissue which has spread out of the bone is found distending the periosteum but still restrained by it or *having violated the periosteum* it may even be found invading the local musculature. Exuberant growth of the myeloma at one bone site, with destruction of the cortex and spread of the tumor beyond the bone in this area, often produces the lesion which first calls attention to the disease, though the marrow of the skeleton as a whole may already be riddled through by tumor tissue. For instance, a patient with multiple myeloma may first present himself because of a localized palpable and often painful enlargement of a rib, a clavicle, a jaw bone, an ilium, or even a long bone of an extremity—particularly a femur or a humerus. The patient showing such a lesion in a femur or a humerus may already have a pathologic fracture at the site of the presenting lesion.



A *B*

Fig. 143.—*A* Calvarium from an autopsied case of multiple myeloma showing multiple lytic defects of varying size. *B* Roentgenogram of an excised block of the same calvarium indicating the rather sharp delimitation of the myelomatous defects. As noted, however this is not a constant finding in multiple myeloma even in cases showing obvious involvement of other bones.

However it is remarkable how often one finds multiple myeloma presenting itself clinically because an exuberant focus of the disease has developed in a vertebral body (or several contiguous bodies) The affected body or bodies are found substantially destroyed Indeed, the tumor tends to transgress them, often producing pressure on the spinal cord or the local nerve trunks, with symptoms resulting In such cases, roentgenographic examination of the rest of the skeleton (including the skull) often fails to reveal the clear-cut, punched-out rarefactions which are conventionally held to distinguish the roentgenographic picture of

multiple myeloma. It is in such cases (especially if one dorsal or lumbar body alone is clearly affected) that the true nature of the disease often goes unrecognized for long periods the lesion frequently being interpreted as a local one i.e. as a hemangioma, a giant-cell tumor a fracture due to Kümmell's disease, or if grossly destructive, as a focus of metastatic cancer The true nature of the disease may become clear if marrow is obtained by sternal puncture or if serial roentgenograms of the rest of the skeleton finally demonstrate widespread lesions in other bones suggesting multiple myeloma, but sometimes it is discovered only at autopsy Eventually *in the far-advanced stage of the disease, the bones of the trunk and* the limbs may become so extensively porotic and deformed from riddling by



Fig 146.—Another instance of multiple myeloma in which there is obvious involvement of the calvarium. It must be borne in mind, however that occasionally metastatic carcinoma may simulate this picture.

neoplastic tissue as to present the appearance of washed-out honeycombed shells roentgenographically However this extreme expression of skeletal devastation is observed only occasionally even at autopsy

In regard to the calvarium, great emphasis is usually laid on the diagnostic value of several or even many roundish, punched-out rarefactions revealed in roentgenograms of the skull It is true that when roentgenograms show clear-cut and widespread involvement of the rest of the skeleton in the form of numerous punched-out rarefactions, the calvarium, too is quite likely to show these, though not infrequently it fails to display them. But it is precisely when one turns to

the roentgenograms of the calvarium because those of the other bones do not show the conventional picture of multiple myeloma that the calvarium, too fails to show it. Whether or not the calvarium shows rarefactions, histologic examination will reveal that the marrow of the diploic spaces has been substantially replaced by the tumor tissue. At sites of clear-cut rarefaction one will find that the tumor tissue is present as a nodule which has encroached on and destroyed the diploic bone, sometimes also thinning the tables, but in our experience the tables are seldom perforated even in such sites. Actually the riddling of the calvarium by tumor deposits, which produces numerous circular punched-out defects, is not invariably an indication of multiple myeloma, since it sometime occurs in carcinomatosis.

Hematologic Observations of Diagnostic Importance

In our cases the hematologic findings were essentially in agreement with those recorded in the literature, which point to the significant frequency with which anemia is encountered with multiple myeloma. The anemia reflects progressive neoplastic encroachment on the myeloid marrow bleeding into tumor tissue, and frequently also the effects of general debilitation and renal damage. About 70 per cent of our patients presented appreciable reduction of hemoglobin and erythrocyte levels when first observed, and in about one half of them the anemia was already of moderate or severe grade. For example, a patient with far-advanced skeletal involvement had a hemoglobin value on admission of only 4.2 Gm. per hundred cubic centimeters of blood and a red blood cell count of 1 400,000 per cubic millimeter In any event, even if the anemia is not profound at first, the trend in most cases followed over a period of several or many months is toward slow but steady decline of the hemoglobin and erythrocyte values, often to appallingly low levels Transfusions, even when repeated, appear to have merely a temporary sparing effect. In a notable case under observation for approximately a year, the hemoglobin value fell as low as 2.6 Gm. and the erythrocyte count to 1 000 000 remaining at about these levels for six months until death resulted from cachexia, renal insufficiency and terminal bronchopneumonia. The profound anemia was reflected anatomically in intense hemosiderosis of liver spleen, marrow and lymph nodes. Incidentally the blood smears showed as many as 20 to 30 normoblasts per hundred white cells counted. The anemia of this particular patient was normocytic, as anemia usually is in cases of myeloma, the color index being slightly below 1 0 but the anemia of some myelomatous patients may be macrocytic in type, simulating pernicious anemia.

The depletion and irritation of the leukopoietic marrow in cases of myeloma are not infrequently reflected by the appearance in the blood smears of a few myelocytes or even myeloblasts and occasionally these immature leukocytes may be present in such large numbers as to produce a leukemoid picture. Thus, multiple myeloma, from a hematologic point of view at least, sometimes simulates myeloid leukemia as first, especially if a purpuric tendency is present. Sometimes, also, the number of eosinophils may be found increased as another indication of

irritation of the marrow. The total leukocyte count shows no consistency and may be normal, somewhat depressed, or slightly increased.

It is pertinent to mention also that any of the following phenomena may be observed in cases of multiple myeloma: excessive rouleau formation in blood smears, autohemagglutination of the red cells in dry and wet films, clumping with Hayem's solution, failure of clot retraction, abnormal viscosity of the blood, and rapid sedimentation rate. It has been shown also that serums from myelomatous patients often have an anticomplementary property, although by no means all such serums give this reaction. These phenomena in general have been ascribed to the presence of hyperproteinemia (which we shall discuss later), and their discovery may afford the first cue to the diagnosis of multiple myeloma.

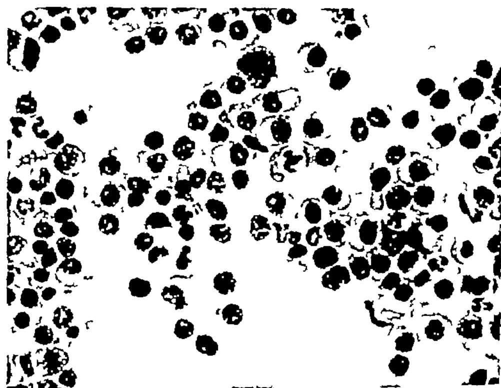


Fig. 147.—Bone marrow spread obtained by sternal marrow puncture of a patient with multiple myeloma. Wright's stain. (×800)

Another important aid in the diagnosis of myeloma through hematologic methods is the finding of myeloma cells or so-called atypical plasma cells in blood smears. The frequency with which such cells are discovered and properly identified (beyond their provisional designation as "blast" cells) seems to depend largely on the thoroughness and skill of the observer, and in suspected cases of myeloma, blood smears should really be scrutinized by a qualified hematologist. They were discovered in only 2 of our cases on routine examination, but Morissette and Watkins claimed to have found them in as many as 41 of 56 cases studied. They pointed out that preliminary scrutiny of the smear under low magnification was necessary for the detection of these abnormal cells.



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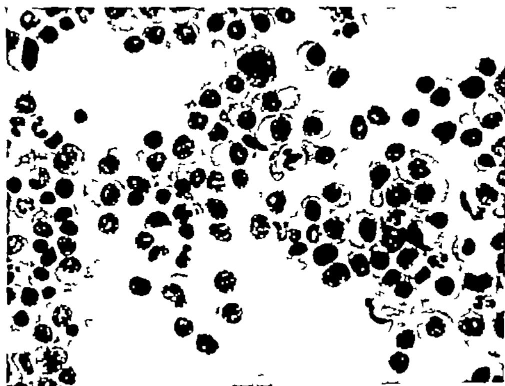


Fig 147—Bone marrow spread obtained by sternal marrow puncture of a patient with multiple myeloma Wright's stain. (×200.)

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In most instances in which they are found the myeloma cells are present in relatively small or at most, moderate numbers, but occasionally there may be such an outpouring of them into the blood stream as to give rise to a frankly leukemic blood picture. Thus in one of our cases (in which transverse myelitis was the cause of death) the leukocyte count during the terminal phase of the disease rose steadily from 6 000 to 40,000 and 30 to 54 per cent of the leukocytes were identified as plasma cells. Such cases of multiple myeloma in which the tumor cells readily invade the blood stream are well known and have been collected and discussed under the head of plasma-cell leukemia by Muller and McNaughton, Piney and Riach Osgood and Hunter Patek and Castle and others. The pertinent cases coming to autopsy indicate conclusively that so-called plasma-cell leukemia has its anatomic foundation in skeletal multiple myeloma and cannot logically be considered, as Osgood and Hunter have suggested, as a disease primarily of the blood. The development of "leukemia" in such cases represents a phase, and often a terminal phase, in the evolution of the disease. It is worth noting that cases of multiple myeloma characterized by frank invasion of the blood stream apparently exhibit a strong tendency toward extraskeletal spread in the form of diffuse and occasionally nodular infiltrations of the spleen, the liver and lymph nodes, and sometimes also of the kidney the pancreas, the skin, or other organs.

Still another valuable diagnostic aid has been advanced in recent years by hematologists, namely the use of sternal marrow puncture. The experience of Rosenthal and Vogel, Beizer and co-workers, Waldenström, and others indicates that sternal puncture has high diagnostic value in cases of multiple myeloma, although it may not necessarily yield positive information in every instance. Certainly it is a procedure that should be employed whenever the presence of myeloma is suspected, and especially when biopsy of some obviously affected bone is not feasible. In most instances of multiple myeloma, according to Wintrobe, cellular marrow spreads will reveal myeloma cells making up 3 to 65 per cent of the total number of cells.

Significant Biochemical Changes in Cases of Multiple Myeloma

Hypercalcemia.—The occurrence of hypercalcemia with multiple myeloma was noted as early as 1927 while the observation that hypercalcuria and a negative calcium balance may be present dates back 35 years or more. Hypercalcemia occurs in about one half of the cases of multiple myeloma, having been observed by us in 8 of the 16 cases investigated (in the remainder the calcium values were within the normal range) The increased calcium values ranged as high as 18 mg per hundred cubic centimeters of serum. It should be noted that in such cases the kidneys tend to show deposits of calcium granules in the tubular epithelium and interstitial connective tissue. In some cases the metastatic calcifications may be quite heavy and widespread, involving in addition, the interstitium of the lungs, the lining of the stomach, and even other tissues.

The increase of calcium in the serum reflects the lytic resorption of the bones and the tendency toward renal failure in many of the cases. It apparently develops

independently of hyperproteinemia, since the highest calcium levels which we observed were in cases in which the serum protein concentration was normal. Apparently, in some instances the tendency toward hypercalcemia is perpetuated and accentuated by secondary hyperplasia of the parathyroid glands developing in response to chronic renal insufficiency. However this mechanism does not invariably operate as Bulger and his co-workers believe. Indeed, in our own autopsies in which the parathyroid glands could be dissected out, these glands did not show significant enlargement.

Hypercalcemia per se is, to be sure, not diagnostic of multiple myeloma even when it is associated with rarefying skeletal lesions, since it also occurs characteristically with idiopathic hyperparathyroidism and occasionally with osteoclastic carcinoma extensively metastasizing to the skeleton. However hypercalcemia associated with either hyperproteinemia or Bence Jones proteinuria is clearly indicative of multiple myeloma. It is precisely because of the presence of hypercalcemia, nephrocalcinosis and resorptive skeletal changes that some cases of multiple myeloma have been misinterpreted as least temporarily as instances of idiopathic hyperparathyroidism, and the patients even subjected to surgical exploration in a misguided search for a parathyroid adenoma. Actually as Jaffe has pointed out, a proper appreciation of the roentgenographic appearance of the calvarium in cases of multiple myeloma should suffice to prevent confusion with hyperparathyroidism, irrespective of the roentgenographic changes elsewhere.

Furthermore multiple myeloma is characterized by the fact that the serum phosphatase activity tends to be normal, no matter how extensive the skeletal involvement may be. It is true that if the serum phosphatase activity is measured shortly after the occurrence of a pathologic fracture, it may be found slightly increased but the increase does not attain the level that is usually reached in advanced stages of hyperparathyroidism. In doubtful cases, in which the skeletal lesions are equivocal roentgenographically the serum protein values are not significantly elevated and Bence Jones proteinuria is not detectable, marrow obtained by sternal puncture should also help to resolve the problem in differential diagnosis.

Hyperproteinemia.—One of the peculiar and characteristic features of some cases of myeloma is the presence of hyperproteinemia, specifically hyperglobulinemia. Indeed, the occurrence of abnormal protein in the blood of patients with multiple myeloma was noted as early as 1899 by Ellinger. Hyperglobulinemia is observed in about half the cases of multiple myeloma. It was present in 8 of 16 cases investigated by us although its incidence is claimed by some to run as high as 60 per cent. The globulin values as determined by the conventional Howe method in these cases ranged between 3 and 14 Gm. per hundred cubic centimeters of blood. The formaldehyde-gel and Takata reactions provide convenient crude tests for hyperglobulinemic serums, but when positive they should be supplemented by precise quantitative methods. The serum albumin does not contribute to the hyperproteinemia, being normal, as a rule, when the globulin value is normal and actually diminished when the globulin value is increased. Thus, in cases of our series in which the serum globulins were normal in concentration the albumin values ranged between 4 and 5 Gm., while in 8 cases in which the globulin (and total

protein) values were increased, the albumin values ranged between 2 and 3.5 Gm. The reason that the serum albumin values are consistently low in the cases of myeloma characterized by hyperglobulinemia seems to be that, in these cases particularly damage of the renal tubules tends to develop, and thus the loss of albumin may conceivably be part of the complex of renal insufficiency.

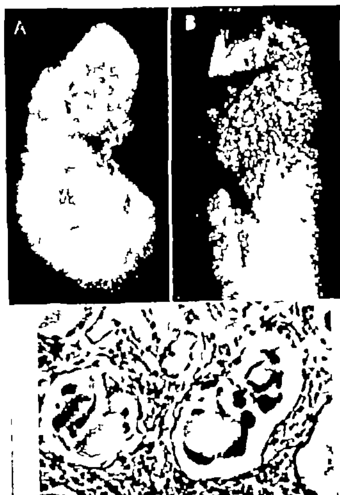


Fig 148.—A and B Roentgenograms from an autopsied case of multiple myeloma featured by extremely rapid demineralization and hypercalcemia, illustrating metastatic calcification (A) in kidney which showed deposits of calcareous material within some of its calices and (B) in lungs which showed grossly evident, yellow gritty deposits of calcium, particularly in the lower lobes. C Photomicrograph from another case of multiple myeloma showing obstruction of renal tubules by protein-containing casts about which there is foreign body giant-cell reaction (×200) (After Lichtenstein and Jaffe, Arch. Path. 44: 207 1947)

Hyperglobulinemia per se is, of course not necessarily indicative of multiple myeloma, since it is known to occur with other conditions also—particularly with chronic infections, notably lymphogranuloma venereum, sarcoidosis and kala azar and occasionally with cirrhosis of the liver chronic nephritis, etc. However hyper

globulinemia should always suggest the possibility of myeloma and, if found in association with hypercalcemia or Bence Jones proteinuria, speaks definitely for myeloma.

The protein composition of myeloma serums has been the subject of active investigation in recent years, and the early studies of Magnus-Levy have been greatly extended by the application of modern electrophoretic methods, which have



Fig 149 – 4 An ostensibly solitary myeloma in the upper femur of an old man. The break in continuity reflects a pathologic fracture that followed open biopsy (Aspiration biopsy often serves to establish a diagnosis in dealing with readily accessible lesions) Although roentgen survey had revealed no other obvious lesions, microscopic foci of myeloma were found in several other bones sampled at autopsy This was true also of two other comparable instances (not illustrated) in which the clinical films had shown only a single large myeloma focus, in a sacrum and in an iliac bone respectively *B* Another initially solitary myeloma focus within a third lumbar vertebral body The lesion was irradiated on the premise that it might represent a giant-cell tumor and it was not until 9½ years later that a shower of myelomatous foci appeared throughout the skeleton

unraveled some of the complexities of the subject. As Wintrobe has summarized with his usual lucidity the solubility characteristics of globulin fractions vary considerably from one patient with myeloma to the next. Most exhibit mobility of gamma globulin, some of beta globulin and a few others of alpha globulin. An additional 20 per cent show only minor abnormalities which are not distinctive

for myeloma. Essentially the same results have been obtained with filter paper electrophoresis. As for Bence Jones protein, so-called, the prevailing view is that this is not a single substance but an ill-defined group of similar proteins.

This multiplicity of Bence Jones proteins and the difficulty of separating them from other normal and abnormal serum proteins make further progress in their identification and assay perplexing although for the detection of small amounts of Bence Jones protein in serum the specific precipitin reaction devised by Hektoen has been employed to advantage. Nor does the complexity of the problem end there. The observations of Wintrobe and Buell, von Bonsdorff Groth, and Packalén, and Shapiro Ross, and Moore indicate that the serums of myelomatous patients



Fig. 150.—Photograph showing the presence of small focal tumor nodules within the ribs, sternum, and vertebral column of an autopsied case of multiple myeloma. It should be borne in mind, however that there are instances of multiple myeloma in which the infiltration of the bone marrow is diffuse and in which there may be no grossly discernible tumor foci.

may on occasion contain still another peculiar abnormal protein substance of high molecular weight and great viscosity differing from Bence Jones protein and showing a tendency to spontaneous precipitation and crystallization. Also noteworthy is the finding in occasional cases of peculiar lipoproteins of cryoglobulin (a cold precipitable serum protein) and of unusual proteins that seemingly interfere with fibrin formation.

Bence Jones Proteinuria.—As is well known, the occurrence in the urine of protein giving the Bence Jones reaction is the earliest recorded observation in connection with the neoplasm now commonly designated multiple myeloma, dating

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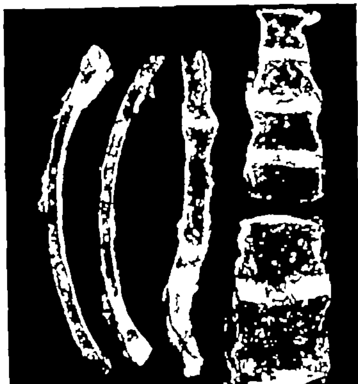


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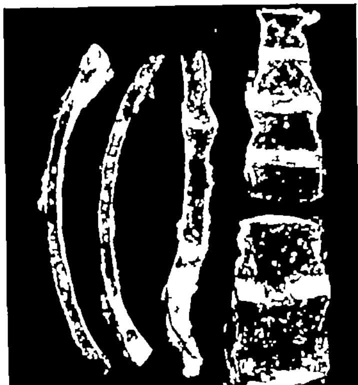


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Bence Jones Proteinuria.—As is well known, the occurrence in the urine of protein giving the Bence Jones reaction is the earliest recorded observation in connection with the neoplasm now commonly designated multiple myeloma dating

back a century It is also generally recognized that the presence of this reaction strongly favors the diagnosis of multiple myeloma (with certain reservations) but that, on the other hand it may be absent in established cases of myeloma. We found evidence of Bence Jones protein in the urine in 10 of 26 cases investigated, although it has been stated that it is found in at least 65 per cent of all cases of multiple myeloma. This discrepancy may be more apparent than real and one must be persistent in searching for Bence Jones protein in the urine, since (1) it may be undetectable in casual specimens but present in a 24-hour specimen, (2) it may be present at certain times but not at others (that is, its excretion may

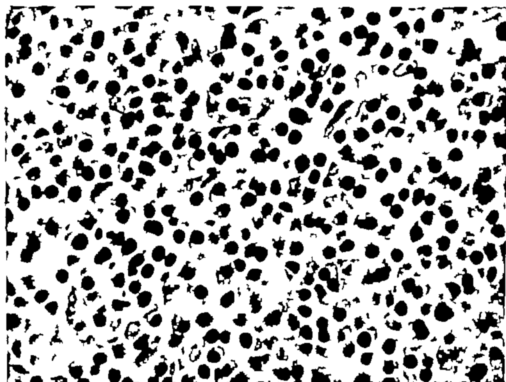


Fig 151.—Photomicrograph of tissue obtained by needle aspiration biopsy of a large tumor focus in a sacrum. (This lesion was the only one observed at the time in the clinical x-ray films, although subsequent autopsy revealed additional foci of myeloma in other bones.) (×500)

be intermittent rather than continuous) and (3) *it may be absent early in the* course of the disease and become evident later on. On the other hand, there are undoubtedly instances of myeloma in which no detectable Bence Jones protein is ever excreted In one of our cases 25 examinations for Bence Jones proteinuria were made over a period of a year all of them yielding negative results, including that made on urine taken from the bladder at autopsy We have not observed any absolute correlation between the cytologic aspects of our myelomas and the incidence of Bence Jones proteinuria, although we do have the impression that the latter

occurs somewhat more frequently with the relatively large cell myelomas (characterized by hyperglobulinemia) than it does with the classic small cell plasmacytoma.

In regard to the specificity of Bence Jones proteinuria it is universally stated that Bence Jones protein may occasionally be found in the urine in certain conditions other than multiple myeloma especially in leukemia and in carcinoma metastatic to the skeleton. However citations of actual experience to that effect are scarce in the literature We have never encountered it in other conditions ourselves, although we have not made any systematic study of the Bence Jones reaction in skeletal diseases other than myeloma There are a few pertinent observations, however—namely those of Boggs and Guthrie, Geschickter and Copeland and Bayrd and Heck—purporting to show that rarely in chronic leukemia and metastatic carcinoma of bone, and still more rarely in certain other diseases of bone (e.g senile osteomalacia, gunshot wound polycythemia) the urine may contain protein giving the Bence Jones reaction. With these exceptions, the finding of Bence Jones proteinuria is, for all practical purposes, indicative of multiple myeloma.

Increased Uric Acid in the Blood.—This represents still another significant, though not specific, change occurring with multiple myeloma. It has been commented on by Stewart and Weber and has been observed by Tarr and Ferris, and also by us in several instances. In the opinion of Stewart and Weber the uric acid increment results from the catabolism of nucleoproteins derived from the myeloma cells—an explanation that seems quite plausible. Multiple myeloma is, of course, not the only tumor responsible for hyperuricemia it is well known for example, that the latter may also occur with the leukemias.

Extraskeletal Myelomatous Infiltrations

As noted, the extraskeletal occurrence of grossly discernible myelomatous foci is decidedly uncommon, although there can be no doubt that in occasional cases of multiple myeloma coming to autopsy (particularly in those in which the blood stream had been invaded by myeloma cells) one may find single or even multiple tumor foci within the internal organs. Microscopic infiltrations, particularly of the spleen, the liver or lymph nodes are somewhat less unusual, but in our experience even these are lacking in most cases of multiple myeloma. Not infrequently what may appear to be independent extraskeletal tumor foci occurring for example, in the dura, the pituitary gland, the oropharynx, and the nasopharynx, the larynx, the thyroid gland the pleura and the retroperitoneal, mediastinal, and subcutaneous tissues may actually represent direct outgrowth of tumor of contiguous bones. Also, in evaluating the reported cases of supposed multiple myeloma characterized by extensive and widespread tumor deposits in the internal organs, it is important to bear in mind that some of them may actually have been instances of metastasizing occult carcinoma, malignant lymphoma, or stem-cell leukemia.

Nevertheless cases of myeloma demonstrating the presence of extraskeletal tumor foci are prominently featured in the literature precisely because of their unusual nature and infiltration of practically any organ that might be named has

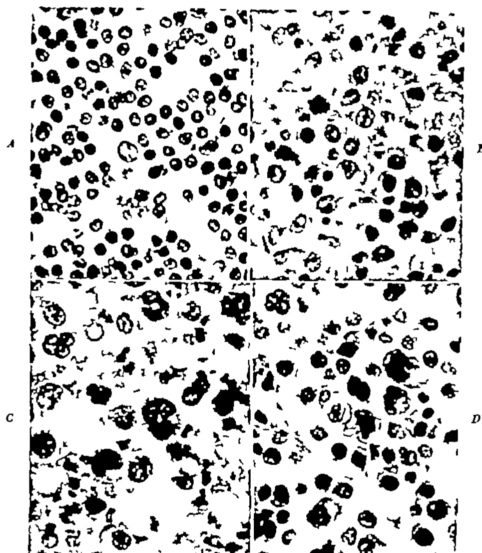


Fig 15.—*A*, *B*, *C* and *D* Photomicrographs further illustrating the cytologic appearance of multiple myeloma *A* Myeloma composed of predominantly small, uniform tumor cells which have a superficial resemblance to plasma cells. Such tumors are frequently designated as plasma cell myeloma or plasmocytoma *B* Another myeloma whose cytologic pattern is dominated by cells considerably larger than those resembling plasma cells, some of which show mitotic figures. *C* and *D* Fields from another myeloma whose cytologic picture is also dominated by comparatively large cells, although there is a sprinkling of smaller cells with nuclei not unlike those of so-called plasma cells. A number of the tumor cells have two or more nuclei, some of which are markedly hyperchromatic It is these large-cell myelomas particularly which are likely to be characterized by hyperglobulinemia and rather often by Bence Jones proteinuria.

been noted at one time or another Thus, Mallory has cited a case of multiple myeloma in which a single metastatic nodule was found in a lung (and also in a bronchial lymph node) and similar instances of pulmonary metastasis have been noted also by Hallermann Carlisle, Piney and Riach and Batts. Metastases have been observed in the heart by Piney and Riach and by Carlisle, who commented on the finding of two discrete bean-sized nodules of myeloma within the wall of the right auricle Nodular infiltrations of an enlarged spleen have been observed by Osgood and Hunter and Churg and Gordon have described a remarkable case in which the spleen (weighing 650 grams) presented innumerable tumor nodules studding and substantially replacing the pulp. In the latter case, infiltration of some of the intra abdominal lymph nodes and of the portal areas and sinusoids of the liver was also noted. Piney and Riach have described the finding of a tumor node the size of a plum, within the pancreas, and Patek and Castle with regard to a case exhibiting "plasma-cell leukemia," commented on the observation of a soft reddish brown tumor node, 1.5 cm. in diameter in the tail of the pancreas. In the latter case incidentally infiltration of the liver the spleen, the kidneys, and the abdominal lymph nodes was also noted microscopically A metastasis in the form of a cherry-sized tumor node has been observed in an adrenal gland by Piney and Riach, and adrenal metastases have been noted by others. Involvement of the kidney has been noted by Carlisle Morse, Donhauser and DeRouville and by Newns and Edwards, the last describing the finding of an essentially circumscribed rounded tumor 4 cm in diameter replacing part of the lower pole of a kidney and bulging into its pelvis. Involvement of the tonsils was noted in an extra ordinary case reported by Jackson, Parker and Bethea, in which a "plasmacytoma" in that region had been removed fully 8 years before generalized involvement of bone could be detected, although the neoplasm had extended to the cervical lymph nodes in the interim. Striking involvement of the intestinal tract has been described by Carlisle, who found numerous tumor deposits in the submucosa of the duodenum and small bowel, the mucosa being tautly stretched over these protuberances. Ovarian metastases have been noted by Herrick and Hektoen, and bilateral tumorous involvement of the male gonads has been observed by Ulrich. Cutaneous involvement in the form of multiple raised nodular infiltrations (scattered over the scalp the region of the clavicle, and the arm) has been described by Duvoir and associates, and Kin has reported a comparable case in which the nodular infil trations (over the face and the back) were large, umbilicated, and ulcerated presenting the general picture of so-called mycosis fungoides. Piney and Riach have described a most unusual case of multiple myeloma with "leukemia" in which the subject presented a diffuse nodular eruption over the trunk and limbs, looking not unlike neurofibromatosis clinically and also a peculiar helmet like thickening ex tending down from the infiltrated scalp of the region of the forehead, in front of the ears, and down to the nape of the neck. Incidentally in this case, as in some of the others characterized by a leukemic blood picture, histologic examination showed infiltration of multiple sites including the cervical lymph nodes, the kidneys, the liver and the heart.

In our own autopsy material we encountered extraskeletal tumor foci only twice. In one instance (in which myeloma cells had been detected in blood smears during life) we encountered a solitary circumscribed whitish nodular focus of myeloma, about 0.5 cm. in diameter within the liver subcapsularly In this case we also observed collections of myeloma cells within the sinuses of the spleen on microscopic examination. In the other case, the lymph nodes along the aorta, within the mesentery at the hilus of the liver and that of the spleen, and around the pancreas were all more or less distinctly enlarged by sheets of tumor cells replacing the normal structure. The liver and the spleen were likewise appreciably enlarged and were seen microscopically to be infiltrated by collections of similar cells. Indeed, the possibility of aleukemic lymphadenosis was at first considered despite a positive Bence Jones reaction, but the observation that the bone marrow was diffusely infiltrated by cells resembling myeloma cells and the finding of renal changes characteristic of multiple myeloma established the latter diagnosis unequivocally

Whether myeloma-cell infiltrations of the liver the spleen, or lymph nodes represent hematogenous metastases of tumor occurring in the bones or rather tumor foci independently formed as a result of activation and neoplasia of potential blood forming cells within the organs in question does not concern us here directly Sometimes infiltration of the spleen and the liver may already be manifested grossly by whitish streaks or nodules, or in the case of lymph nodes, by diffuse enlargement and cellularity but more often it is detected only on microscopic examination. On the other hand, our experience definitely runs counter on that of Lowenhaupt, who claimed to have found "plasma cells" of myelomatous nature in every one of the spleens from 12 patients who came to autopsy in all of the lymph nodes examined and 3 of the livers as well. Similarly Gordon and Churg felt that they had established the presence of extraskeletal tumor foci in 22 of 30 cases studied. It should be pointed out, however that the indubitable identification of isolated small nests of cells presumed to be myeloma cells and their clear-cut differentiation from cells of histiocytic or inflammatory nature commonly encountered in the spleen and the lymph nodes, particularly may be exceedingly difficult. Apparently we were more conservative than other observers in the matter of accepting such cell nests as tumor foci. Furthermore, as Mallory has rightly emphasized, small collections of immature blood cells representing foci of compensatory extramedullary hemopoiesis are observed rather frequently in cases of multiple myeloma, and these may also be mistaken for nests of myeloma cells.

Significant Renal Changes in Cases of Multiple Myeloma

In the patient with multiple myeloma there are certain cytologic renal changes of almost pathognomonic distinctiveness. These changes may be manifested clinically in more or less heavy albuminuria, though not necessarily Bence Jones proteinuria and in diminished power of the kidney to concentrate and to clear nitrogenous constituents. Only exceptionally do they result in the development of edema or hypertension. It has been emphasized on that account (Foord and others) that the finding of "atypical nephritis" should always suggest the possibility of multiple

myeloma. When the renal damage is limited in extent, it results clinically in no more than persistent albuminuria. On the other hand, when it is more severe it often leads ultimately to progressive renal insufficiency Occasionally it leads to the relatively early appearance of azotemia which dominates the clinical picture before the presence of multiple myeloma is even suspected

Already in 1921, Löhlein noted the deposition of crystalloid hyalin-like casts in the renal tubules of a subject with multiple myeloma coming to autopsy Many of the casts plugging the tubules were surrounded by polymorphonuclear leukocytes, and often also by giant cells, which Löhlein thought were derived from proliferated tubular epithelium. There was some dilatation of the tubules, also some interstitial scarring, but the glomeruli and the blood vessels were not remarkable. The specificity of these essential changes was confirmed by Perla and Hutner Ehrich, Bell Fishberg, Forbus and co-workers, Morison, Blackman and his co-workers, Newns and Edwards, and others. Indeed, Mallory and his colleagues spoke of the "myeloma kidney" and maintained that it is often possible to make a diagnosis of multiple myeloma from observing the kidney sections alone.

Grossly in our 18 autopsies the kidneys were usually not remarkably altered. In 2 instances, however they were found to be markedly contracted as a result of extensive interstitial scarring On reviewing the sections of kidneys obtained in the autopsies we, too were impressed by the constant finding of rather dense eosinophilic hyalin-like plugs of proteinaceous material in the renal tubules, particularly in the lower portions of the nephrons. In about half of the kidneys examined, one could find foreign body giant cells or clumps of polymorphonuclear leukocytes, or both about the casts, although at times one had to search for them. In some instances the proteinaceous plugs were rather scattered, but in others they were numerous. It is pertinent in this connection to recall the exceptional case reported by Holman, in which the tubular obstruction was extensive enough to result in complete urinary suppression. It is noteworthy that the characteristic tubular plugs were found by us in cases in which the Bence Jones reaction had been negative as well as in those in which it had been positive. It seems altogether probable that abnormal proteins other than Bence Jones protein are also precipitated out in the tubules. We observed no significant glomerular changes in our material, although it may be noted in passing that Foord emphasized the possible role of obstruction of glomerular capillaries by highly concentrated protein or by clumped erythrocytes as a factor in the development of renal insufficiency We did, however observe degenerative changes in the tubular epithelium in a number of the kidneys, as evidenced by the granular vacuolar or hyaline droplet appearance of the lining cells and a tendency toward desquamation.

Some of the kidneys also exhibited a number of other changes worthy of mention. In several slight to moderate arteriosclerotic contraction was noted (which must be evaluated in the light of the fact that these subjects were older adults) In one kidney pyelonephritis was present, having followed on compression of the spinal cord and ascending infection of the urinary tract. In another what appeared to be amyloid in granular or droplet form was present within the tubular epithelium and lumens though not in the glomeruli. In one (in a case of far

advanced myeloma featured by rapidly progressing, extreme demineralization of the skeleton and hypercalcemia, the calcium amounting to almost 18 mg) evidence of deposition of calcium was observed grossly as well as microscopically In this kidney (there was also heavy metastatic calcification of the lungs) one could recognize yellowish streaks within some of the pyramids, and fine yellowish calcific gravel was present in many of the calices and within the urinary bladder as well.

Amyloidosis in Relation to Multiple Myeloma

Another arresting feature of the pathologic anatomy of multiple myeloma is the presence of amyloid in some cases. Atkinson found amyloidosis complicating myeloma in 40 to 643 cases of myeloma collected from the literature. On this basis the incidence is about 6 per cent. In our own material it was about 10 per cent. The presence of amyloid, particularly since it seems to occur in association with hyperglobulinemia and Bence Jones proteinuria, affords ground for speculation as to the chemical relations which may exist between the abnormal blood proteins and the amyloid protein substances. It has been suggested that the abnormal blood proteins may serve as the mother substance of the amyloid proteins and that the amount and the distribution of the amyloid are determined also by disturbed fibroblastic activity Whatever the mechanism of amyloid formation may be in the body in general, it does seem probable that excessive formation of abnormal globulins is an essential condition for the deposition of amyloid, and it is conceivable that the latter represents a reaction to the foreign proteins in question.

As far as the skeleton is concerned, if amyloid is found, it usually appears in the form of scattered deposits detectable only microscopically in the neoplastic tissue of the affected bones. In an occasional case, however one finds not only the microscopic deposits but large agglomerations of amyloid intermingled with and substantially replacing myelomatous foci. In Freund's case the amyloid took the form of multiple calcifying amyloid tumors, one of which, breaking out of the seventh dorsal vertebral body had produced extradural compression of the cord. The presence of multiple myeloma as a basis for the amyloid tumors in this case was recognized only on microscopic examination, there having been no grossly discernible tumor nodes within the bones but rather a diffuse infiltration of the marrow In this case the amyloid was entirely limited to the skeleton. On the other hand, we have observed a case of so-called atypical amyloidosis in which autopsy failed to reveal evidence of amyloid in the myelomatous tissue itself, though practically all the extraskeletal tissues and organs, including the voluntary muscles and the skin were heavily infiltrated with amyloid.

In general, one of the striking features of amyloidosis appearing in association with multiple myeloma is the frequency with which amyloid is deposited in unusual sites, either more or less diffusely or in the form of tumorlike masses which may attain large bulk. In contrast to the commonplace amyloidosis of parenchymatous organs (particularly the liver the spleen, the adrenal glands, and the kidneys) one may find amyloid deposited in great quantity in bones, in muscles, in joint capsules and in the skeletal connective tissues generally in the skin and subcutaneous tissue, in the buccal and anal mucous membranes, in the tongue, in the

heart, in the lungs, in the intestines in the genitourinary tract and in other tissues. Indeed, so often is multiple myeloma the basis for so-called atypical or idiopathic amyloidosis that the possibility of myeloma should be investigated in every case even though the bones present no apparent evidence of tumor either roentgenographically or on gross inspection at autopsy

These cases of unusual amyloidosis are all of great interest, but we may single out certain ones for special comment. In one of our cases involvement of the skin and subcutis led to remarkable sclerodermalike thickening and the occurrence of amyloid-containing verrucae, which were found on the eyelids about the anus, on the oral mucous membrane and along the margins of the enlarged rubbery



Fig. 133 – Photomicrograph showing amyloid deposits within a focus of multiple myeloma. The tumor cells in the background cannot be distinguished at this low magnification. (×125)

ulcerated tongue. Also noteworthy are the cases in which the mucosa or the muscular coat of the small intestine is extensively infiltrated by amyloid, since this deposition may lead at times to clinically puzzling intestinal obstruction. Of particular interest, also are the cases standing out because of the presence of multiple, smaller or larger localized amyloid masses attached to the periosteum of the bones, especially near their articulations, and situated also in the skeletal muscles of the trunk and the extremities and about and within joint capsules. In relation to the latter the amyloid may extend to the synovium and sublining tissue and at times, even erupt into the joints. Among the regions that may be selected are the hands, the antecubital fossae, the shoulders, and the articulations of the clavicle The presence of such joint swellings, associated with pain and limitation of motion,

sometimes leads to a clinical diagnosis of rheumatoid arthritis, which may be entertained for years before the nature of the condition is recognized. The amyloid masses seen in these cases are described as having a firm, grayish yellow or pinkish, lardaceous or glassy appearance somewhat suggestive of the flesh of fish, and microscopically they present as amorphous, poorly cellular generally eosinophilic aggregates, about which one may observe foreign body giant cells. It is noteworthy also that this amyloid material either in part or throughout, may fail to give the usual metachromatic staining reactions with one or another or perhaps all, of the dyes commonly employed for the detection of amyloid.

Relationship of Apparently Solitary Myeloma and Multiple Myeloma

As has been stated, there are occasional cases of myeloma in which the first skeletal manifestation is that of an exuberant tumor focus within some one bone (commonly a femur or a humerus, but sometimes a vertebral body an innominate bone, a bone of the calvarium, or some other bone) and in which clear-cut roentgenographic evidence of implication of other bones does not appear for a number of years. We have observed a number of such cases. In one of them attention was at first centered on an apparently solitary neoplastic focus in the third lumbar vertebral body Indeed, this lesion was irradiated as a possible hemangioma or giant-cell tumor It was not until 2½ years after the onset of symptoms that a veritable shower of foci of myeloma appeared throughout the skeleton. In another case the presenting focus (identified by biopsy as a myeloma) was a large tumor apparently localized within the upper end of the right femur This tumor had transformed the upper part of the shaft, the intertrochanteric region, and the neck into a ballooned-out, rarefied and coarsely honeycombed lesion simulating a peculiar cyst or giant-cell tumor Roentgenograms of the pelvis and the upper ends of the femurs (the only roentgenograms taken at the time) showed, otherwise, merely equivocal involvement of the right ilium and suggestive rarefaction shadows within the greater trochanter region of the left femur This patient received radiation therapy at another hospital with clinical improvement resulting The case was subsequently included among those reported by Coley who likewise interpreted it as one of solitary myeloma. From him we learned that the patient died after a terminal wasting illness suggesting dissemination of tumor but not until she had survived almost 10 years after the onset of complaints referable to the tumor of the femur Many other cases of supposedly solitary myeloma have been reported, including some with entirely inadequate follow up records, and have attracted attention because they tended to controvert the conventionally doleful prognosis for myeloma in general. Among the more detailed and informative of these reports are those of Bailey Pasternack and Waugh and Stewart and Taylor citing survivals of 7 7½ and 8 years, respectively in patients who were still alive and apparently in good health at the time of publication. Christopherson and Miller have also stressed the favorable outcome of (ostensibly) solitary myeloma, but a 3-year period of observation as a criterion for localization is hardly adequate. The consensus with regard to treatment seems to be that roentgen therapy has con-

siderable value in affording relief from pain and possibly also in retarding local growth and eventual dissemination of the tumor.

In regard to these initially localized myelomas, it is hardly possible to determine from the available evidence whether the tumor in any given instance was entirely confined to the skeletal focus first attracting attention or whether it was already present elsewhere in the skeleton but clinically and roentgenographically silent. It has been claimed by the advocates of the former view that the negative result of roentgenographic examination of the remainder of the skeleton affords proof of the solitary nature of the myeloma in question. However it is well known that the marrow throughout the skeleton may be extensively permeated by myeloma without this being evident roentgenographically. The long period of latency is also cited as proof but, as we have seen, there is no certainty when dealing with such a tumor that foci of myeloma may not appear throughout the skeleton at any time. Indeed as such cases are followed the number of survivors falls off steadily from year to year so that at the end of a 10 year period of observation few ostensibly solitary myelomas are left. Also cited as proof of actual one-bone localization is the absence of anemia and of Bence Jones proteinuria, but these are hardly trustworthy indications.

A more valid criterion would be sternal marrow punctates showing absence of myeloma cells—a test which was resorted to in few of the cases held to represent genuine solitary myeloma—but even this is not infallible. When one turns to the pertinent autopsy reports in the literature for more satisfactory proof of the existence of genuine solitary myeloma, one finds that there have been few in which the skeleton was examined with sufficient thoroughness both grossly and microscopically to exclude convincingly the possibility that myeloma occurred in other bones. It is true that on the basis of cases such as those reported by Harding and Kimball, Rutishauser and Raven and Willis one has to admit the possibility of there being a genuine solitary myeloma, but the condition must be quite rare. All one can say with certainty is that there are occasional cases in which myeloma starts out by producing an exuberant tumor focus in some one bone, commonly a long bone, and then tends to remain latent (in spite of pathologic fractures) for a long time, sometimes even as long as 10 years, without giving rise to clearly discernible foci in other bones. The great likelihood is that in such cases the myeloma, if followed for a sufficiently long time, will eventually show obvious dissemination.

Following another tangent, it may be mentioned in passing that Johnson and Meador have presented observations suggesting that on occasion lesions of inflammatory histiocytosis may simulate "benign solitary myeloma," so-called.

Cytologic Character of Multiple Myeloma

The tumor tissue in multiple myeloma (when its appearance is not modified by hemorrhage, degeneration and necrosis, fracture of the bone or extension of the tumor into the soft parts) tends characteristically to be composed of large aggregates or veritable sheets of more or less compacted cells without any discernible intercellular material and without conspicuous supporting stroma. However where

the bone marrow is being invaded by tumor one observes marrow cells intermingled with tumor cells which as they proliferate, tend to crowd out and eventually replace the marrow constituents. In selecting material for sectioning, one should choose some blocks of solid tumor tissue (relatively free of secondary changes) which do not require decalcification, since treatment with acid tends to shrink the cells and to darken and obscure nuclear detail. Most of our histologic preparations were stained with hematoxylin and eosin, though some were dyed with eosin-methylene blue, which seems particularly well suited to bringing out cytologic detail.

It has been recognized and must be emphasized that the cytologic picture is not the same in all specimens of multiple myeloma. Roughly however the tumors can be fitted into two general cytologic groups. On the one hand, there are those in which the tumor cells are quite uniform and predominantly small and have a superficial resemblance to plasma cells. The tumor cell is roundish and has a stippled nucleus substantially filling the cell The darkish chromatin particles spotting the nucleus are dispersed centrally as well as peripherally, and one actually observes nothing resembling a cart wheel in the sense of spokes radiating from a hub. The cytoplasm tends to be uniformly eosinophilic, though in occasional tumors one may observe lighter-staining perinuclear demilunes. Interspersed among these cells there may be some cells which, though of the same general character are larger in respect to both cytoplasm and nucleus. There may also be occasional cells with double nuclei, but there is no tendency to cellular irregularity otherwise. It is to the myeloma showing this cytologic character that the name "plasma-cell myeloma" or plasmacytoma" is commonly applied (although these names have come to be rather indiscriminately applied to most myelomas, even to those in which the tumor cells have only the remotest resemblance to plasma cells)

In the other group of myelomas the cytologic picture tends to be dominated by cells larger than those resembling plasma cells, but may be a rather variegated one. The dominant cells in the tumor generally exceed the myeloblast in size and, on the whole, show fairly abundant cytoplasm and have a large, round oval, or even reniform, pale stippled nucleus. The latter is not necessarily eccentric and indeed is often centrally placed. In some tumors the nuclei of certain of the cells may contain a well-defined pinkish or reddish round body resembling a nucleolus. The cytoplasm is generally eosinophilic but sometimes takes a more basophilic or polychromatic tinctorial hue, and in some tumors it also presents paler demilunes around the central face of the nucleus. Occasionally the cytoplasm is vacuolated or contains refractile rod-shaped bodies, considered by some to be of protein nature. In any particular tumor site examined, one may also find some of the smaller cells resembling plasma cells or on the other hand, find cells which are much larger than the dominant ones and frequently show nuclear atypism. Specifically such atypical cells may present large and hyperchromatic nuclei of bizarre shape or two or more nuclei.

Among the tumors in our material there were also a number which cytologically seemed to be intermediate between the predominantly small-cell and large-cell myelomas. These tumors resembled the small-cell tumors in that they presented

considerable cellular uniformity however their cells had somewhat larger nuclei on the whole, and there were an appreciable number of cells with very large nuclei and more than very occasional cells with two or more nuclei

Correlation of the cytologic appearance of the myelomas in our material with the pertinent biochemical data especially with the serum protein values (in those cases in which these values had been determined) yielded some interesting results. Specifically we had 4 myelomas classed as large-cell myelomas according to the criteria just outlined and 2 that were intermediate in type, and with all of these the serum globulin values were significantly elevated while the corresponding serum albumin values were diminished. On the other hand there were 5 myelomas classed as small-cell myelomas by the same criteria, and with all of these the serum albumin and globulin values were well within the normal range As previously noted, Bence Jones proteinuria was observed with both cytologic types though it was found more often with large-cell myelomas. Hypercalcemia was observed about as frequently with one type as with the other

It would appear from these data that the cases of large-cell myeloma in particular are characterized by hyperglobulinemia. If this trend should be substantiated by further observations we would have at least some insight into the puzzling question as to why hyperglobulinemia is observed in certain cases of multiple myeloma but not in others. Specifically it would seem plausible that globulins may be produced or stored in appreciable quantity within the large and apparently less mature tumor cells and, by the same token liberated and mobilized by way of the blood stream as these cells are broken down.

It is pertinent at this point to consider whether or not the large and small tumor cells, respectively represent essentially different types of cells as far as their derivation is concerned. This question may not be of as great practical moment as it would be if for instance it had been established that the myelomas of relatively mature histologic appearance respond more favorably to treatment or necessarily pursue a more prolonged course than do the others It is, however germane to a better understanding of the nature of the neoplastic process. We are inclined to doubt whether there is any essential difference save one of maturity between the large and small tumor cells, since the predominantly large-cell myelomas contain smaller cells in some places, to which it is possible to trace transitions, and the predominantly small-cell myelomas contain occasional large cells. We would emphasize instead the unity of multiple myelomas and explain cytologic variations within them as expressions of their relative maturity or immaturity This is the concept that has been advocated by Wallgren in particular One may draw a parallel with malignant lymphomas among which one observes some composed of relatively small, mature lymphocytic cells, others composed of somewhat larger less mature lymphoblastic cells, and still others composed of quite large, immature reticulum cells of more variable appearance all of them derived from a common lymphoid stem cell.

The identification of the common ancestral cell of multiple myeloma, however is still a moot point. Some have held that the tumor cells of multiple myeloma are abnormal hematic cells whose origin may be traced to the primitive reticulum

cell of the bone marrow and this theory has much to recommend it. Others have been impressed in certain cases by the alleged resemblance of the tumor cells to myeloblasts or myelocytes, to lymphoblasts or lymphocytes, to erythroblasts, to mature or immature marrow plasma cells, to megakaryoblasts, or to hemocytoblasts.

Be that as it may it should be emphasized that multiple myeloma presents a characteristic clinico-anatomic picture, centered around the skeletal manifestations of the disease and their sequelae, and that, with rare exceptions, this picture is readily distinguishable from that presented by any of the other neoplasms of hemopoietic derivation. So distinctive is multiple myeloma as a single and basically uniform disease complex that one is at a loss to understand why in some quarters it has been subclassified, presumably on the basis of cell type, into plasma-cell, myeloid, erythroid and lymphoid myeloma. Indeed there can be little doubt that multiple myeloma as discussed in this paper is a disease of unitary cell type, the variations in cytologic appearance reflecting stages in the maturation of the basic tumor cell. Specifically regarding the histogenesis of multiple myeloma, we are inclined to hold with Wallgren, Wood and Lucké, Wintrobe and others that this neoplasm consists of distinctive tumor cells which are probably of myeloid formative or hematic origin (though not clearly resembling any normal marrow cells or their immediate precursors) and are best designated noncommittally as myeloma cells.

Cognizance must also be taken of the idea stemming from von Rustizky and Lubarsch that multiple myeloma represents a systematized disease of the hemopoietic apparatus and, as such, is not a true neoplasm but rather a hyperplasia related to the 'leukemias. There can be no serious objection to holding that multiple myeloma is akin to chronic myelosis and malignant lymphoma in the sense that it, too belongs to the general family of neoplasms of hematic origin, although, as has already been indicated it presents definite clinico-anatomic characteristics that sharply delimit it from these diseases. However it is difficult to understand, even on theoretic grounds, how multiple myeloma can be regarded as anything but a malignant neoplasm in the face of widespread formation of tumors within the skeleton the tendency toward perforation of the cortices of affected bones and extension into the adjacent soft parts, the capacity of its cells to invade the blood stream and to metastasize to the viscera generally in addition to involving the hemopoietic organs, and the consistent trend toward a fatal termination.

Treatment

Problems in therapy are concerned mainly with palliation, particularly the relief of distressing bone pain, general supportive measures, and the handling of such complications as fractures and compression of the spinal cord. In regard to general supportive measures, the use of repeated transfusions to combat anemia when this is present and the avoidance of prolonged bed care should be emphasized. The consensus of radiotherapists seems to be that roentgen therapy if judiciously employed frequently though not invariably has value in palliation but that it has relatively little influence otherwise on the course of the disease except possibly when one is dealing with what appears to be a solitary myeloma.

Experience with radioactive phosphorus (P^{32}) in the treatment of multiple myeloma is still limited but is sufficient to indicate what may be expected at best and what its limitations are. In some patients, but by no means all, radiophosphorus therapy has resulted in appreciable subjective clinical improvement evidenced chiefly by relief of pain permitting restoration of more normal activity. Apparently no concomitant significant change in the roentgenographic appearance of the skeletal lesions has been observed. Reinhard and associates concluded from their survey that radioactive phosphorus has not proved to be a really valuable therapeutic agent for the treatment of multiple myeloma and that the latter does not respond as favorably to that agent as it does to roentgen radiation. Indeed, it was felt that radiophosphorus therapy had shortened the life expectancy of 2 patients by producing severe leukopenia and thrombocytopenia. Radiostrontium (Sr^{89}) has also been tried therapeutically, though without encouraging results.

The administration of Stilbamidine (4,4-diamidinostilbene) and Pentamidine (4,4 [pentamethylene dioxy] dibenzamidine) in conjunction with a diet low in animal protein has been advocated by Snapper for the treatment of patients with multiple myeloma, especially those with widespread but not large osteolytic lesions and with normally functioning kidneys. In such patients he claimed to have observed a favorable influence on excruciating bone pain, but stated that the lesions persist and that treatment at best only checks the disease temporarily and does not cure it. Snapper pointed to the appearance of granules within the cytoplasm of the myeloma cells as an indication of the specific action of Stilbamidine on these cells. The drug, however, has certain toxic effects, including injury of the trigeminal nerve in some cases, which is manifested in the development, following a delay, of facial anesthesia, and it seems that before employing the drugs in question for their palliative effect, one would be well advised to try first roentgen therapy in order to achieve the same result. Urethane (ethyl carbamate) is also capable of effecting symptomatic improvement in patients with multiple myeloma, although its long range results do not engender any great enthusiasm.

Aside from treatment of fractures, especially those of long bones, surgical intervention has a place in the relief of transverse myelitis resulting from extradural compression, which is accomplished by laminectomy. In regard to the latter, Jacox and Kahn, and Batts have shown that this procedure, if followed by roentgen therapy, may permit complete recovery of function and even survival thereafter for a number of years. They emphasized that laminectomy should always be done before roentgen therapy is given, in order to prevent further damage being done to the cord by swelling subsequent to irradiation. Also, the question of ablation of a limb for myeloma sometimes arises, but only in connection with the comparatively rare, ostensibly solitary myeloma of a long bone. In cases of this type, as noted, one can never be certain that tumor is not present in other bones in spite of their negative roentgenographic appearance. It is pertinent, however, to cite the remarkable case reported by Stewart and Taylor. The patient was alive and well 8 years after forequarter amputation for a huge myeloma which had largely destroyed the upper third of the shaft of a humerus and was freely invading the muscles of the upper arm.

Summary

Multiple myeloma represents a clinically and pathologically distinctive malignant disease of the skeleton primarily which apparently takes its departure from the hematic cells in the bone marrow and occasionally in other extraskeletal sites. Anatomically practically every bone may ultimately come to be involved more or less in a given case. The skeletal progress of the disease may be steady and rapid, sometimes from the beginning and sometimes after a static period. In some cases, also before the disease becomes spread over the skeleton it may flourish in one bone (as a so-called solitary myeloma) for months or even years. Though at autopsy the skeleton may be found riddled through with foci of myeloma, it is only infrequently that gross foci are found in the viscera and other extraskeletal parts. Nevertheless, even in the absence of gross infiltrations, microscopic examination sometimes reveals smaller or larger numbers of myeloma cells within the spleen, the liver or lymph nodes, and occasionally in other organs as well. Also, in some cases, myeloma cells may invade the blood stream. Ordinarily under these circumstances, relatively few myeloma cells are found in the blood smears but in an occasional case they may be so numerous as to create a leukemic blood picture (so-called plasma-cell leukemia)

Although there are these points of resemblance to other neoplasms of hematic origin it should be emphasized that multiple myeloma presents a characteristic clinico-anatomic picture centered around the skeletal manifestations of the disease and their sequelae, and that *with rare exceptions this picture is readily distinguishable* from that presented by any of the other neoplasms of hemopoietic derivation. In this connection we have stressed the diagnostic significance of hypercalcemia, hyperglobulinemia (and its associated hematologic manifestations) and Bence Jones proteinuria, the not infrequent presence of atypical amyloidosis in association with myeloma and the well known cytologic renal changes of almost pathognomonic distinctiveness. The latter result commonly in more or less heavy albuminuria and often in renal insufficiency of a peculiar type. In regard to amyloidosis it was indicated that multiple myeloma is so often the basis for atypical amyloid deposits that the possibility of myeloma should be investigated in every case of idiopathic amyloidosis, even though the bones present no evidence of tumor either roentgenographically or on gross inspection at autopsy

The tumor tissue in multiple myeloma tends characteristically to be composed of large aggregates of more or less compacted cells without any discernible intercellular material and without conspicuous supporting stroma. It has been recognized and must be emphasized that the cytologic picture is not the same in all specimens of multiple myeloma. Roughly however the tumors can be fitted into two general cytologic groups. On the one hand, there are those in which the tumor cells are quite uniform and predominantly small and have a superficial resemblance to plasma cells. It is to the myeloma showing this cytologic appearance that the name "plasma-cell myeloma" or "plasmacytoma" is commonly applied. In the other group of myelomas the cytologic picture tends to be dominated by cells larger than those resembling plasma cells, but may be a rather variegated one. The

dominant cell shows fairly abundant cytoplasm and has a large round oval or even reniform, pale stippled nucleus. In any particular tumor site examined one may also find some of the smaller cells resembling plasma cells, or on the other hand one may find cells which are much larger than the dominant ones and frequently show nuclear atypism. Specifically such atypical cells may present large and hyperchromatic nuclei giant nuclei of bizarre shape or two or more nuclei

We are inclined to doubt whether there is any essential difference, save one of maturity between the large and the small tumor cells So distinctive is multiple myeloma as a single and basically uniform disease complex that one is at a loss to understand why in some quarters it has been subclassified, presumably on the basis of cell type into plasma-cell, myeloid erythroid, and lymphoid myeloma. Indeed, there seems to be little doubt that multiple myeloma as discussed in this paper is a disease of unitary cell type, the cytologic variations reflecting stages in the maturation of the basic tumor cell. Specifically regarding the histogenesis of multiple myeloma, we are inclined to hold with Wallgren and others that this neoplasm consists of distinctive tumor cells which are probably of myeloid formative or hematic origin (though not clearly resembling any normal marrow cells or their immediate precursors) and are best designated noncommittally as myeloma cells.

Correlation of the cytologic aspects of the myelomas in our material with the pertinent biochemical data strongly suggests that it is the large-cell myelomas particularly which are characterized by hyperglobulinemia and, rather often by Bence Jones proteinuria.

On the clinical side, in our cases of multiple myeloma we found that the great majority of the patients were between 40 and 60 years of age, though some were in their 30's, and one was only 13 years old when the first manifestations of the disease appeared. Our data indicate that multiple myeloma may be slightly more prevalent in males than in females, but do not support the often repeated statement that the condition is at least twice as frequent in males. In regard to the roentgenographic findings, we found that the picture conventionally held to distinguish multiple myeloma—that of many bones, including the calvarium, riddled by clear cut punched-out osteolytic defects—represents the exception rather than the rule and applies only to certain cases in which the disease is far advanced. Indeed, very often one observes merely some vaguely defined rarefactions in a number of the bones or a single exuberant tumor focus in some one bone (commonly a femur or a humerus, but sometimes a vertebral body a rib or a clavicle, an innominate bone, a bone of the calvarium, or some other bone) without obvious involvement of the skeleton generally Sometimes (when myelomatous infiltration of the marrow is diffuse) skeletal changes may not be apparent at all roentgenographically or the replacement of the marrow by tumor may be reflected merely by some osteoporosis. As for the calvarium, this not infrequently fails to show numerous punched-out rarefactions, even when roentgenograms show clear-cut and widespread involvement of the rest of the skeleton. In such equivocal or initially obscure cases one must utilize fully all the available diagnostic cues to arrive at a combination of significant findings constituting probable or conclusive evidence of the presence

of multiple myeloma. Marrow obtained by sternal puncture is often of great value in establishing the diagnosis.

Multiple myeloma has too variable a clinical course to permit of any dogmatic statement in regard to prognosis. It is true that the average length of survival after the onset of symptoms is not likely to be more than about 2 years. However there are occasional patients with multiple myeloma, particularly those in whom the disease was apparently localized at the outset, whose course may be protracted over a number of years, sometimes as long as 10 years or more. Problems in therapy are concerned mainly with palliation, particularly the relief of distressing bone pain and general supportive measures, also the handling of such complications as fractures of bones and compression of the spinal cord.

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XIX

Skeletal Manifestations of Other Tumors of Hematopoietic Origin

In this rather concise consideration of a complex subject, the emphasis, as noted, is placed entirely upon skeletal manifestations in keeping with the scope of this monograph. For a comprehensive discussion of the leukemias, both acute and chronic, and of the various expressions of malignant lymphoma in their broader aspects, the reader is referred to the standard hematology texts of Wintrobe, Sturgis, and others, and to selected reviews dealing with these subjects.[8, 23]

Chronic Myeloid Leukemia

It is well known that in chronic myeloid leukemia (chronic myelogenous leukemia, chronic myelocytic leukemia, chronic myelosis) the bone marrow throughout the skeleton is regularly and more or less extensively replaced, as one might expect, by proliferating cells of the myeloid series. However there may be no symptoms directly referable to this skeletal involvement, except for the finding in many cases of localized tenderness (elicited by pressure) over the sternum, a clinical sign emphasized by Craver as being of some diagnostic value. Roentgenographically also one fails as a rule to detect any discernible evidence of diffuse marrow infiltration. This is true even of roentgenograms of autopsy specimens, of the vertebral column for instance, which afford optimum clarity of detail (Fig 156) On gross inspection of such specimens a uniform grayish coloration of the marrow is generally the only significant alteration noted. It should be noted however as Snapper has emphasized, that in rare instances of the disease one may observe the formation of smaller or larger discrete localized tumor nodes within one or more affected bones e.g the ribs, the vertebrae a femur or an innominate bone, as the case may be[8, 27, 31]

It may be relevant here to comment briefly upon the occasional finding of diffuse osteosclerosis and myelofibrosis in association with splenomegaly and a blood picture simulating that of myeloid leukemia. It was formerly held that the skeletal changes indicated might represent a burned-out end stage of a true leukemia. However in more recent papers[1, 12, 14, 21] dealing with such cases, this view has been challenged and the prevailing interpretation is rather that of a primary or idiopathic osteosclerosis and marrow fibrosis leading to myeloid exhaustion extensive compensatory extramedullary hemopoiesis in the lymph nodes, liver and spleen (so-called agnogenic myeloid metaplasia) and the concomitant appearance of immature leukocytes and erythrocytes in the peripheral blood.



Fig 154. Fig 155

Fig 154.—Roentgenograms reflecting skeletal changes of acute leukemia in a child.
Fig. 155.—Early skeletal changes in leukemia in a child. Note irregular rarefaction zones adjacent to epiphyseal cartilage plates (suggestive of the diagnosis, though not pathognomonic)

Acute Leukemias

In the acute leukemias (which may be of lymphoblastic, myeloblastic, monocytic, or of more undifferentiated stem-cell type) the clinical and especially roentgenographic manifestations of skeletal involvement take on diagnostic importance and are commonly observed, particularly in infants and children. This is rather what one might expect in dealing with a group of relatively aggressive and rapidly progressive or even fulminant, hematic neoplasms. In such cases, osseous involvement is frequently manifested clinically in bone pain and tenderness, limitation of motion, and ostensible arthritic symptoms attributable to juxta-articular leukemic infiltration. Before the presence of leukemia is recognized these skeletal

manifestations, considered in association with anemia and fever may plausibly *suggest osteomyelitis, brucellosis, sepsis, rheumatic fever or Still's disease*, as the case may be. On roentgen skeletal survey if attention is not focused altogether upon a single region distinctive changes may be observed in a significantly large number of cases in the long bones, the pelvis, the vertebral column, the calvarium, and even in the hand bones These roentgenographic findings have been discussed at length by Silverman, and Kalayjian, Herbut, and Erf, among others. Specifically one may observe multiple, ill-defined or more clearly punched-out areas of rarefaction in affected bones, for example in the shafts of long bones, where the

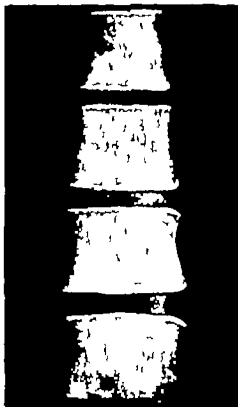


Fig 156.—Roentgenogram of several vertebral bodies from an autopsied case of chronic myeloid leukemia showing no discernible alteration even though the marrow is everywhere diffusely infiltrated.

spongiosa or corticalis has been focally destroyed. In some instances, these osteolytic lesions may be found in association with concomitant, focal, or more diffuse reactive osteosclerosis. In relation to these osseous defects also there is often discernible *periosteal new bone apposition ("onionpeel" effect), developing as a reaction* to penetration of the cortex by leukemic cells. Among the other significant changes which have been described in acute leukemia are the presence of juxta-epiphyseal transverse radiolucent bands, pathologic fractures and dislocations, compression of one or more vertebral bodies, and partial destruction of epiphyses, especially collapse of a capital femoral epiphysis (Figs. 154 and 155)

Specific mention should also be made of the striking skeletal changes observed in chloroma (an unusual aggressive form of acute or subacute leukemia occurring particularly though not exclusively in children) in which the tumor deposits present an evanescent greenish coloration said to be due to protoporphyrin In chloroma, one may encounter not only conspicuous periosteal new bone formation but also sizable subperiosteal and parosteal tumor masses developing in relation to the vertebral column ribs, calvarium, and other bones. In the skull particularly there may be extension into the base of the cranial vault the paranasal sinuses, and especially the orbits, giving rise to proptosis and conspicuous tumorous protrusions, comparable to those sometimes observed in children with disseminated neuroblastoma.[16, 17] I have observed material from a pertinent case in an adult in whom the clinical picture was at first dominated by signs of optic nerve impairment (shown eventually to have resulted from aggressive infiltration at the base of the brain



Fig. 157.—Roentgenogram of a segment of the shaft of a femur from an autopsied case of chloroma (myeloblastic leukemia) This aggressive neoplasm had extended through the cortex and periosteum into the adjacent soft parts. This is not apparent in the x-ray picture which does, however show appreciable rarefaction of the femur and moth-eaten erosion of its cortex in places.

by chloroma) It was not until some months had elapsed that hematologic examination including sternal marrow puncture revealed the presence of myeloblastic leukemia (Fig 157)

As has already been indicated, plasma-cell leukemia, so-called, seems clearly to represent a leukemic phase, often a terminal one, of multiple myeloma. As such the pathologic changes associated with it have been discussed under the head of multiple myeloma (Chapter 18)

"Lymphosarcoma"

This section deals briefly with the skeletal changes observed in lymphocytic, lymphoblastic, and reticulum-cell lymphoma, whether or not these are associated

with a blood picture of lymphatic leukemia. The latter in keeping with the concept of Gall and Mallory is interpreted not as a pathologic entity but rather as an incidental phase, often a late or terminal one, in the evolution of malignant lymphoma (or lymphosarcoma in the older terminology)

On the whole, extensive infiltration or replacement of the bone marrow by proliferating tumor cells is not nearly as constant in lymphosarcoma as it is in chronic myeloid leukemia. Moreover, it is only in occasional instances that osseous involvement is sufficiently outspoken to be recognized roentgenographically and published estimates of their incidence range from about 7 to 25 per cent. While one may sometimes observe a compressed vertebral body (Fig 158) or a lytic



Fig. 158.—Roentgenogram of a segment of the vertebral column from an autopsied case of chronic lymphatic leukemia showing a compressed vertebral body

defect in one bone or another, e.g., the calvarium or a limb bone, involvement of the bone marrow when present does not lead as a rule to grossly discernible, discrete tumor nodes and therefore becomes clearly evident in most instances only on microscopic examination. The tumor deposits microscopically may occasionally take the form of focal nodular aggregates, but more often they are less circumscribed and rather diffusely infiltrating The extent of marrow replacement by tumor is likewise variable, and may be rather limited or on occasion, so pronounced as to have resulted clinically in myelophthisic anemia. The cytology of the tumor foci in the bone marrow in any particular case reflects that of the neoplastic process generally and, as noted, depending upon their stage of maturation, the cells may

be predominantly lymphocytic, lymphoblastic, of reticulum-cell type, or occasionally more polymorphous in character. It may be mentioned in passing that the occurrence of bone marrow involvement in lymphosarcoma need occasion no surprise, since even in normal bone marrow one not infrequently finds isolated collections of lymphocytes, if one searches for them.



Fig. 139.—Roentgenogram showing multiple lytic defects in a case of generalized lymphosarcomatosis, simulating those of multiple myeloma. Extensive skeletal involvement such as this is exceptional, however.

The presence of localized skeletal lesions of sufficient size and destructiveness to be detectable roentgenographically is more likely to be encountered in dealing with the reticulum-cell sarcomas than with the more differentiated lymphosarcomas. In surveying their extensive material pertaining to malignant lymphoma, Gall and Mallory found that clinically discernible skeletal lesions, representing in many instances an apparently solitary manifestation of the disease, had been noted in one-fourth of the patients with "clasmatocytoma" (a subdivision of reticulum-cell sarcoma). Such skeletal foci were observed less frequently in lymphoblastic lymphoma and were distinctly unusual in lymphocytic lymphoma. It is pertinent to

note also that clinically significant skeletal involvement may be encountered in some instances of follicular lymphoblastoma. Thus, Meyer in surveying 6 cases in point found roentgenographically discernible osseous involvement in 2, in one of which there was an obvious destructive focus in the lower shaft of a femur In the same connection, it is relevant to cite the remarkable case of "polymorphous-cell sarcoma" reported by Kenny which apparently represents an instance of reticulum-cell sarcomatous developing as an end stage of giant follicular lymphoblastoma and involving the lymph nodes and the gastrointestinal tract as well as the bones. Virtually the entire skeleton showed osteoporosis and vaguely mottled, moth-eaten rarefactions and in fact, the patient's presenting complaints related to the occurrence of multiple pathologic fractures (Fig 159)

Primary Reticulum-Cell Sarcoma of Bone

The occasional finding of apparently localized skeletal involvement as the sole, or at least initial manifestation of what appears to be reticulum-cell sarcoma (clasmatocytoma, monocytoma) deserves further consideration because of the possibility of clinical cure in such cases by appropriate therapy As established by Parker and Jackson and subsequently confirmed by others, there can be no doubt that such instances do occur from time to time and that cures can be obtained by radical surgery in selected cases in which the tumor is situated in an accessible site (usually a limb bone) and has not as yet come to involve the regional lymph nodes or spread to distant parts. There is further evidence to indicate that roentgen therapy in moderate dosage may effectively destroy such tumors. There is also sound evidence to indicate that even in pertinent cases in which fatal dissemination does occur eventually clinical remission for a number of years may be obtained by resorting to surgical ablation and/or irradiation. The publication in recent years of sizeable groups of documented cases from a number of large centers has fully substantiated the soundness of the concept of primary reticulum-cell sarcoma of bone and has afforded much information of value in regard to diagnosis and treatment.

In 1939 Parker and Jackson, on the basis of a study of 17 pertinent cases, many of them culled from the Bone Sarcoma Registry directed attention to the tumor under consideration, which they held to be distinctive and, in particular different from Ewing's sarcoma. They further expressed the view that this neoplasm was derived from the reticulum cells of the marrow of the affected bone and that its cell type was identical with that of reticulum-cell sarcoma of lymph nodes and other hematopoietic tissues. In regard to cytologic detail, it was emphasized that many of the tumor cells present ovoid, reniform, or horseshoe-shaped nuclei, suggesting ameboid activity In this connection, it is significant also that the tumor cells at times display a striking tendency to phagocytose leucocytes. These are features, one might add, that hardly characterize the cytology of Ewing's sarcoma. It is also pertinent to point out in regard to nomenclature that the designations of primary reticulum-cell sarcoma of bone,[12] clasmatocytic lymphoma,[10] and monocytoma[11] seem clearly to have reference to essentially the same neoplasm.

Clinically the tumor under discussion presents as a painful, often extensive but localized, destructive lesion prone to pathologic fracture. When it arises in a long bone, as is often the case, the end of the bone and much of the shaft tend to be involved. The roentgenographic picture may be suggestive of the diagnosis to an observer who has had personal experience with the lesion, as emphasized by Sherman and Snyder but on the whole, it lacks any sharp or specific distinctiveness which would enable one to distinguish it clearly from that of other more differen-

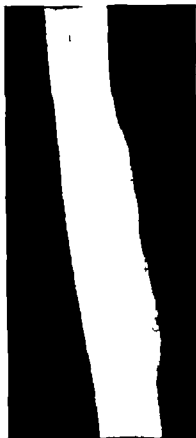


Fig. 160.—Roentgenogram of a tumor in the shaft of the femur of an adult woman which proved on biopsy to be a reticulum-cell sarcoma. The picture here is not one of destructive mottling, but rather that of localized cortical thickening, with periosteal new bone reaction. The extent of marrow involvement is not too clear. Roentgen irradiation afforded complete relief of symptoms; the patient was well 2 years later and her progress is still being followed.

tiated lymphomas, Ewing's tumor or osteolytic osteogenic sarcoma. Roentgenograms of a lesion which has not been previously irradiated are likely to show vaguely mottled rarefaction and possibly some widening of the affected bone area. There may be insidious penetration of the cortex by tumor and extension into the contiguous soft parts or into a neighboring joint (e.g., a knee or a shoulder joint) without provoking any conspicuous periosteal new bone apposition. In order to establish a definitive diagnosis of the presenting tumor one must resort to biopsy

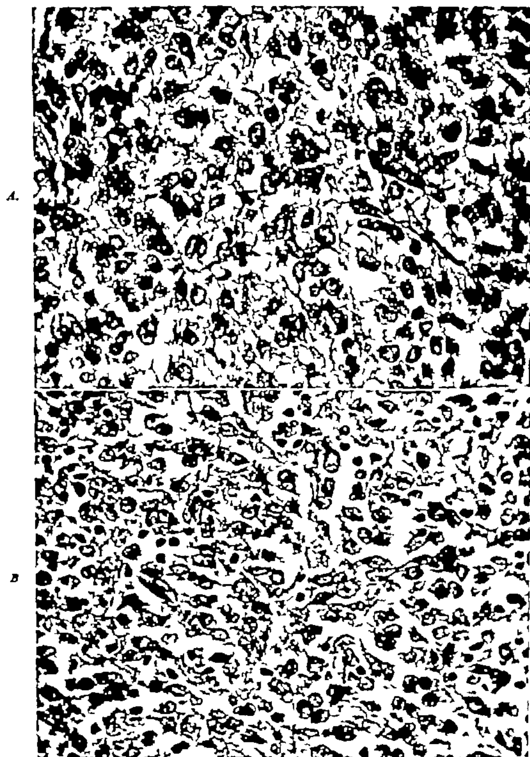


Fig 161.—*A* and *B* Photomicrographs of 2 representative instances of primary reticulum cell sarcoma of bone marrow. The picture is not unlike that of reticulum-cell sarcoma elsewhere. On the other hand, it differs in a number of essential respects from that of Ewing's sarcoma (compare with Fig 135 taken at the same magnification, ×475)

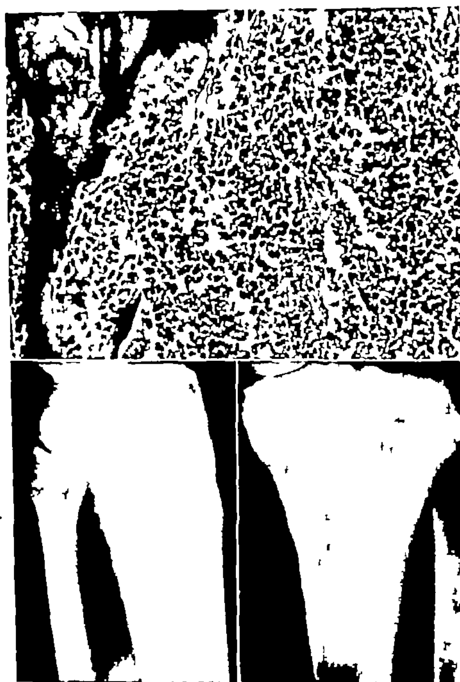


Fig. 162.—*A* Photomicrograph of a representative field of an irradiated necrotic reticulum cell sarcoma in the upper end of a tibia, the roentgen pictures of which are illustrated in *B* and *C* The tumor had been biopsied and then received 2000 r In all of the numerous sections examined one observed merely the ghost outlines of necrotic tumor cells. (×225) *B* and *C* Lateral and anteroposterior views of the irradiated reticulum-cell sarcoma shown in *A* This patient was apparently well and free of tumor at the follow up 4 years later

Before instituting treatment, however a roentgen skeletal survey should be made, and any enlarged superficial lymph nodes that may be present should also be examined.

Since this book last went to press (some five years ago) I have had occasion to observe material from 10 instances of primary reticulum-cell sarcoma of bone. Although the pertinent data have little statistical validity they happen to be in line with trends observed in substantially larger published series. It is interesting to note, therefore, that, with two exceptions, the patients were comparatively young, in the first, second and third decades and that all but three presenting lesions were in long limb bones. The three exceptions were encountered in a rib, a metatarsal bone, and the sacroiliac region, respectively In two instances of long bone involvement, pathologic fracture had ensued prior to treatment. X ray irradiation was recommended in all instances in which treatment had not already been instituted, but insufficient time has elapsed for the results to have much meaning

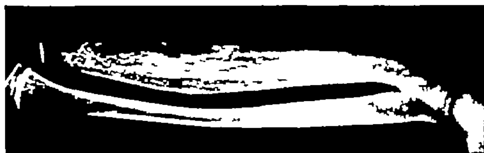


Fig 165—Roentgenogram of another irradiated focus of reticulum-cell sarcoma in the distal half of an ulna. (The diagnosis was based upon a pre-irradiation biopsy) This patient subsequently manifested another tumor focus in a tibia.

In regard to therapy Parker and Jackson have advocated prompt radical surgery (amputation of the affected limb in most instances) as a curative measure, followed by prophylactic irradiation of the regional lymph nodes. They further expressed the view that roentgen therapy in itself in lieu of surgery is inadequate. Of the 17 patients whose cases were discussed by them, 7 who had received appropriate treatment were alive and apparently free of tumor 10 years or more later In those patients who survived for a shorter period, there were indications of subsequent involvement of regional lymph nodes and eventual widespread dissemination of the tumor That this sanguine experience is not unique is evidenced for example by the reports of Hatcher reflecting the experience of the University of Chicago Clinic and of Coley citing that of the Memorial Hospital. In both series of cases cited, survival well beyond 5 years was observed in as many as half of the patients treated.

The validity of the opinion expressed by Parker and Jackson that roentgen therapy for reticulum-cell sarcoma of bone is necessarily inadequate may now be questioned with some justification. Aside from empirical clinical observations indicating the apparent effectiveness of irradiation per se, both Hatcher and Coley have cited pertinent instances in which examination of an affected bone which

had been irradiated prior to excision failed to show any viable residual tumor In this connection also, I have had occasion to examine a tibia which had been the site of a reticulum-cell sarcoma as established by biopsy The patient had previously received a total tumor dose of approximately 2,000 r following which amputation was nevertheless performed with a view to cure (skeletal survey did not reveal any additional lesions), since some doubt had been raised as to the efficacy of the roentgen therapy It is therefore significant to note that, although the medullary cavity of the affected proximal end of the tibia was extensively permeated by necrotic tumor, nowhere in any of the numerous sections examined did



Fig 164—Roentgenogram of a primary reticulum-cell sarcoma of the lower fibula in a young patient. In this instance there was local recurrence after roentgen irradiation and eventually below knee amputation had to be done (In our experience of recent years, failure of irradiation is the exception, rather than the rule)

this tumor tissue appear viable (Fig 162) Coley Higinbotham, and Groesbeck have also stressed the relatively high degree of radiocurability in those patients in whom clinically discernible distant metastases have not occurred prior to therapy Specifically they estimated the 5-year survival rate for this group at 73 7 per cent and the 10-year rate as high as 55 per cent. In any individual patient, however one must be cautious in the matter of prognosis, even though the therapeutic response is gratifying, since the appearance of tumor foci elsewhere may be delayed as much as 5 to 10 years or more. Incidentally Coley and his associates advocate

a total tumor depth dose as high as 3 000 to 4 000 r (even though a substantially smaller dose in the neighborhood of 2 000 r can be effective) in the belief that this tends to minimize the possibility of local recurrence.

It is relevant to remark at this point, by way of summary that altogether the natural course of the tumors under discussion is certainly not that of Ewing's sarcoma. *In particular, the localized* character of many of these tumors, their tendency to involve regional lymph nodes eventually and their gratifying response to appropriate therapy resulting in a high percentage of 5 to 10 year cures are quite unlike the behavior of Ewing tumors in which cures are seldom obtained even following prompt surgical ablation and in which roentgen therapy achieves only local amelioration without significantly inhibiting early dissemination throughout the skeleton or pulmonary metastasis. The differentiation, therefore, between primary reticulum-cell sarcoma of bone and Ewing's sarcoma is of more than academic import and rests upon a more substantial basis than subtle cytologic differences.

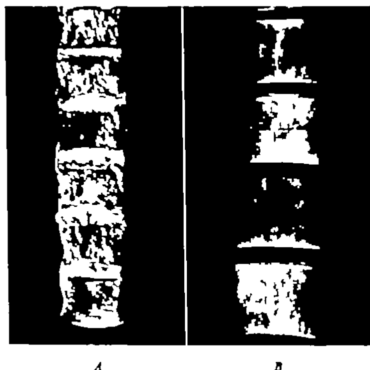


A. *B.*

Fig 163—*A* Roentgenogram showing a lesion in the upper end of a humerus which proved on biopsy to represent a focus of Hodgkin's disease Evidence of periosteal new bone reaction is the only clue afforded by the x ray picture, which indicates the malignant nature of the lesion. This patient also presented marked widening of the mediastinum. *B* Another rather nondescript, lesion in an ischium which likewise proved to be a focus of Hodgkin's disease. From the mottled rarefaction and erosion of the cortex, one might suspect a malignant lesion although not necessarily Hodgkin's disease This patient also presented a collapsed vertebral body

Hodgkin's Disease

Hodgkin's disease exclusively limited to a single bone marrow focus or even to the marrow as a whole, without concomitant involvement of hematopoietic tissues elsewhere must be very rare if it exists at all, and I have never observed such an instance. In the same connection, it may be noted that Gall and Mallory in their extensive survey of malignant lymphoma (of all types) covering 193 cases of Hodgkin's disease and 36 of Hodgkin's sarcoma, did not record a single instance in which initial localization in some one bone was observed. However bone marrow involvement as part of the picture of more or less disseminated Hodgkin's disease



A B

Fig. 166—*A* and *B* A case of Hodgkin's disease in which although every vertebral body is riddled with tumor there is no roentgenographic indication of extensive skeletal involvement. (See also Fig. 167)

is rather common, although here again, as in other expressions of malignant lymphoma, there are many cases in which this cannot be detected on roentgenographic skeletal survey. Thus, as indicated by Falconer and Leonard published estimates of the incidence of skeletal lesions in Hodgkin's disease as determined by roentgen examination fall in the range from 7 to 26 per cent (averaging about 15 per cent) whereas comparable estimates as determined by autopsy[30] range between 40 and 78 per cent). This wide deviation may reflect random sampling, but more likely it is the fact that some examiners are more thorough than others in their search for skeletal foci. The higher figure is more in keeping with my experience. I find that as random cases of systematized Hodgkin's disease come to

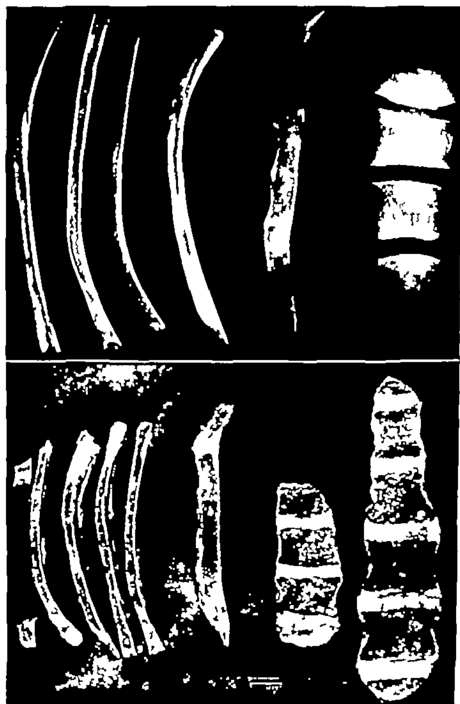


Fig 107 — *A* and *B* Roentgenogram and corresponding photograph of portions of the vertebral column, sternum, and several ribs from an autopsied case of Hodgkin's disease showing extensive skeletal, as well as visceral, involvement. Although these bones were riddled with tumor foci, there is no tangible evidence of their presence in the roentgenogram of the specimen.

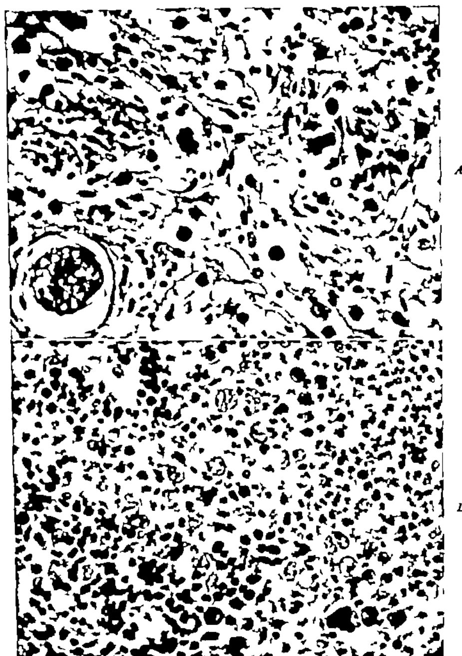


Fig. 168.—*A* Photomicrograph of a preserved field within a lesion of Hodgkin's disease in a vertebral body (autopsied case). The classical picture of Hodgkin's disease as seen in lymph nodes is usually not observed in bone marrow sites, and the diagnosis may sometimes be rather difficult. (It is interesting to note the fortuitous finding of a small nerve bundle in the field in the lower left hand corner.) (×325.) *B* Photomicrograph of an unusual lesion of Hodgkin's disease in a sternum which simulated a focus of eosinophilic granuloma (the polymorphonuclear leukocytes in the field were eosinophiles), although the large cells, some of which are multinuclear, did suggest a malignant neoplasm. It was not until the patient developed a packet of enlarged lymph nodes that the diagnosis of Hodgkin's disease became obvious. (×220.)

autopsy one case is likely to show no discernible foci at all within the bone marrow (at least of the vertebral column sternum and ribs) a second a limited number of grossly evident, yellowish foci within a number of bones and a third, riddling of the skeleton by many such foci.

As noted, roentgen examination of the involved bones fails to reflect this involvement in most instances, despite the sharp detail afforded by roentgenograms of actual specimens (Figs. 166 and 167) It is only when the lesions happen to destroy or erode cortical bone or having penetrated the cortex, provoke periosteal new bone apposition, or in the case of the spine, bring about compression or collapse of a vertebral body that there is any tangible evidence of their presence. When such lesions are detected (and they may be encountered in innominate bones, the vertebral column, and in flat bones, as well as long bones) their roentgenographic appearance is rather nondescript, and while one may think in terms of some neoplasm, one is not likely to suspect the correct diagnosis prior to biopsy unless the patient also happens to present mediastinal widening, enlarged superficial lymph nodes, or a palpable abdominal or retroperitoneal mass (Fig 165)

The recognition of Hodgkin's disease in a bone biopsy specimen often presents a difficult problem, because the picture tends frequently to be masked or distorted by necrosis and secondary inflammatory reaction. This may be true not only of needle aspiration biopsies, but also of tissue obtained by open operation. To cite a case in point, I recall a biopsy specimen from a collapsed vertebral body (discovered after an injury) in which the underlying lesion was so obscured by extensive necrosis that it was virtually impossible to venture any definitive diagnosis. It was not until some time afterward when the patient developed a packet of enlarged axillary nodes that examination of the latter established the diagnosis of Hodgkin's disease, and at autopsy some months later widespread visceral as well as skeletal involvement was demonstrated. At other times, it is true, one may discern multinucleated cells apparently of reticular origin, associated with an inflammatory reaction and appreciable fibrosis but again it may not be a simple task on the basis of such evidence alone to distinguish clearly between Hodgkin's disease and other expressions of malignant lymphoma (Fig 168 *A*)

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XX

Liposarcoma of Bone

The occasional occurrence of a lipoma of bone in the sense of a circumscribed benign tumor of adult fat cells within fatty bone marrow should rather be expected, theoretically at least, although I have never observed an example of it. A number of lipomas within vertebral bodies have been reported by Makrycostas, but Schmorl was inclined to discount these as conspicuous circumscribed foci of fatty marrow rather than genuine neoplasms. Several other case reports in the older literature have been cited by Dawson. Haas also made casual mention of "a few authentic cases" of lipoma of bone marrow but cited no specific references that can be verified. Recently Dickson and his associates published a well-documented instance of an intramedullary lipoma situated in the lower end of a tibia, and cited two additional cases in the older literature. Within the past several years several additional pertinent cases have been recorded by Caruolo and Dahlin, by Child, and by Skinner and Fraser These comparatively rare medullary lipomas are of no great practical moment apparently except in so far as they may be mistaken clinically for more serious neoplasms.

The development in bone of malignant neoplasms of ostensible fat-cell derivation has also been noted. At any rate, a limited number of tumors so regarded have been reported within the past 20 years. The concept of an unusual and distinctive primary tumor of bone that may be logically interpreted as a liposarcoma has been sponsored by Ewing and Stewart and their associates at the Memorial Hospital, and the relatively few recorded cases in point have been inspired by or have emanated from that source with one notable exception, that of a case reported recently (1955) by Dawson of Edinburgh, which will be discussed farther on. Thus, Coley in his recent monograph indicates his belief in the existence of primary liposarcoma of bone, as distinct from liposarcomas of skeletal soft parts which have eroded or invaded the adjacent bone secondarily although, at the same time, he expresses Stewart's admission that the evidence is largely circumstantial. On the other hand this concept has not met with general acceptance by others and in

particular, W G Barnard and also Stout have questioned its validity Altogether the existence of a primary liposarcoma of bone appears to have been a debatable question.

The first report dealing with ostensible liposarcoma of bone marrow and its recognition as such is credited to Ewing (1928) The same two cases along with another were subsequently published by Stewart, and additional pertinent instances were later placed on record by Fender L. Barnard, Rehbock and Hauser and Duffy and Stewart. In his classification of bone tumors prepared for the Bone Sarcoma Registry (1939), Ewing[10] unequivocally accepted liposarcoma as a distinctive tumor arising from the fat cells of bone marrow In that connection, he remarked that "there had been few examples of this characteristic tumor recorded, but enough to warrant its inclusion in the present classification," adding further that "this tumor is probably more frequent than is now recognized" It is relevant to note also that Geschickter and Copeland have cited two cases which they regard as liposarcomas of long bones (one occurring in the lower femur of a 19-year-old boy the other in the humerus of a girl 14 years old) although in neither case did they offer any convincing proof of the identity of the tumor as liposarcoma.

Clinically the neoplasms in question appear to represent peculiar osteolytic tumors developing in the shafts of long limb bones. They are characterized by more or less extensive destruction of the cortex of the affected bone area, pathologic fracture, and extension into the contiguous soft parts. They are said further to be appreciably radiosensitive, though exhibiting a tendency to spread ultimately after an interval of some years, to other skeletal sites. On gross inspection, the tumor tissue of a pertinent specimen may not suggest fat origin particularly although on microscopic examination, in some parts of the neoplasm at least, one may observe vacuolated tumor cells containing sudanophilic droplets. Inasmuch as tumor cells other than lipoblasts may phagocytose or otherwise come to contain fat droplets, it is obviously difficult on that basis alone to establish convincingly the identity of an alleged liposarcoma, unless the tumor cells generally clearly resemble embryonal fat cells.

Through the courtesy of Dr Kenabey of Los Angeles, I have had occasion to review the case of a peculiar malignant bone tumor which was considered tentatively to represent a possible liposarcoma and which serves to highlight the rather difficult problem in differential diagnosis. The patient, a 46-year-old woman, presented initially a markedly expanded and faintly trabeculated, radiolucent lesion in the lower shaft of a fibula which had been painful for some 3 months. There was no indication of periosteal new bone apposition in the roentgenogram, although the lesion had markedly attenuated the expanded cortical shell. At exploration, undertaken after a short intensive course of roentgen therapy firm pinkish white tumor tissue was encountered, cytologically resembling a sarcoma of essentially spindle-cell orientation. It was elected to resect the fibula rather than amputate, following which procedure, surprisingly enough, the patient remained well clinically for fully 5 years. Eventually however she manifested tumor extension to the ipsilateral femur as well as a rib a scapula, the vertebral column and the right lung Altogether the patient survived 7 years after resection of the

tumor in the fibula. At autopsy, tumor tissue was said to have been present in the skeletal sites indicated, and otherwise, only in the right lung and the adjacent chest wall. This case is not unlike those reported by Stewart and his associates as instances of liposarcoma and has in common with them the unusual location, and roentgen appearance of the presenting tumor appreciable radiosensitivity, the delayed appearance of tumor in other bones, and finally visceral metastases. On microscopic examination, the tumor cells, in some fields at least, appeared vacuolated, and their nuclei were compressed against the cell membranes by intracellular material which was sudanophilic, so that they had some resemblance to fat cells.

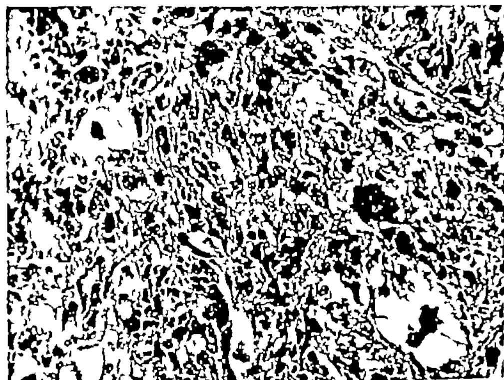


Fig 169—Photomicrograph of a field of a primary sarcoma in the intertrochanteric region of the femur of a young man in his twenties. The cytology of this tumor and especially the presence of large, bizarre vacuolated tumor giant-cells strongly suggested the possibility of liposarcoma. (×220)

Presumably the long duration of the clinical course and the autopsy findings in this case rule out the likelihood of metastatic tumor (from an anaplastic carcinoma of the kidney for example) On the other hand, if the tumor in the fibula represents a primary sarcoma, one wonders whether it should be regarded as a liposarcoma or rather as some other slowly growing undifferentiated sarcoma that happens to contain lipid in places.

In this connection, it is relevant to cite the remarks of Stout, expressed at a Tumor Seminar held at the State Cancer Hospital in Missouri in April, 1949 as follows "The question of whether or not liposarcoma can develop in bone

marrow is still open to debate. You may recall that some years ago Fred Stewart reported several cases of what he called liposarcoma of bone and following that report there were *some more from various people* I took occasion to find out that in each one of those reports the diagnosis of liposarcoma was confirmed by Dr Stewart at the Memorial Hospital so really he is the protagonist of that diagnosis. *Now he has decided he tells me that he was probably wrong in calling those* tumors liposarcomas he no longer believes they are liposarcomas, and he does not know what they are" This appears to be valid criticism of the series of ostensible "liposarcomas" of bone *reported in the 1930 decade, and the precise nature of* these particular neoplasms, whatever they may be is still apparently undetermined. There is other more convincing evidence, however to support the concept of primary liposarcoma of bone Some years *ago I had occasion to observe a fat-containing* mesenchymoma of bone arising within the upper tibia, which, in spite of prompt amputation, metastasized freely to the lungs and mediastinum shortly thereafter In this case, both the *primary tumor and its metastases contained abundant unmistakable* embryonal fat associated with prominent aggregates of lymphoid cells osteogenic sarcoma being the other major component The large fields of fat tissue were clearly *recognizable as such even in the gross being pale yellow and distinctly* greasy It appears to me that, if neoplastic tissue of malignant fat-cell origin can develop as a major integral part of a primary mesenchymoma of bone there is no good *reason a priori why it should not, on rare occasions, take the form of a pure* liposarcoma. That it may in fact, do so is clearly demonstrated by the carefully documented and well illustrated case in point reported by Dawson (1955) that of a primary *malignant neoplasm of the lower shaft of a femur of a young woman* 28 years of age, which invaded the contiguous soft parts and proved fatal from pulmonary metastasis, despite prompt disarticulation. The evidence presented in support of the *interpretation of primary liposarcoma of bone should convince even* the most skeptical observer Incidentally this was the only neoplasm of its kind seen in the University Laboratory at Edinburgh over a period of 26 years.

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XXI

Chordoma

Chordoma is one of the rarer primary neoplasms of the skeleton and of the vertebral column particularly which apparently results from neoplastic proliferation of notochordal remnants persisting within the nucleus pulposus of intervertebral discs, and probably also of aberrant chordal vestiges within the vertebral bodies themselves.* As is well known, this tumor develops most often at the ends of the axial skeleton that is, in the sacrum and/or coccyx, or in the vicinity of the spheno-occipital synchondrosis or the clivus of Blumenbach (where occasionally also a non-malignant excrescence of notochordal tissue the so-called ecchordosis physa Ephora," may be encountered) In fact, the sacrococcygeal and the basi-cranial sites account for fully 90 per cent of all the reported instances of chordoma. It should be noted, however that occasional instances have been encountered also in the lumbar and even the dorsal and cervical regions of the vertebral column (although one must be certain in such cases that one is not dealing actually with chondrosarcoma) For example, in the slide set of the Armed Forces Institute of Pathology dealing with brain and spinal cord tumors, there is a section of a chordoma which occupied portions of the bodies of the seventh, eighth, and ninth dorsal vertebrae and extended also into the vertebral attachment of the right seventh rib. Survey of the literature of recent years shows reports continuing to appear of relatively unusual chordomas at the lumbar dorsal, and cervical levels of the vertebral column, as well as of the more common ones in the sacrococcygeal region and the cephalad end of the axial skeleton. Among these, the paper by Congdon furnishes a good deal of pathologic detail of value, supported by clinical correlation.

Whatever its situation may be, chordoma is a locally invasive tumor which tends to destroy and replace the bone at its site of development. By the time it comes to clinical notice, it has usually extended also into the contiguous soft parts, giving rise eventually to bulky intrapelvic, intra-abdominal, or intracranial growths, as the case may be.

A



B

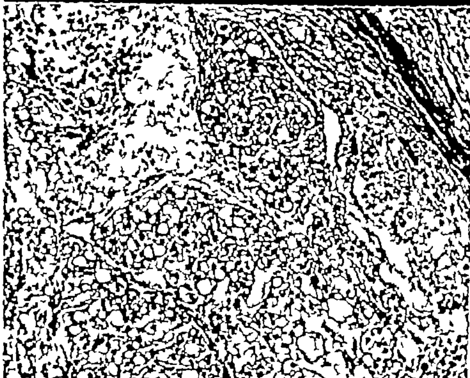


Fig 170.—*A* Roentgenogram of a lytic tumorlike lesion in the coccyx and lower sacrum which proved to be a chordoma. The appearance of the lesion is rather nondescript, although its location might lead one to suspect the presence of a chordoma. The patient, a 38-year-old man, had complained of obstipation and presented a palpable mass over the coccyx, which could also be felt through the compressed rectum *B* Photomicrograph of a representative field of the chordoma illustrated in *A* showing the presence of peculiar vacuolated mucin containing (physaliferous) tumor cells (×110)

In the majority of instances the tumor grows relatively slowly, often over a period of years, and manifests no disposition to metastasize even late in the course of its evolution and after one or more unsuccessful attempts at local excision. It should be noted however that there are occasional instances of chordoma particularly in the sacrococcygeal region which pursue a more aggressive course and give rise to widespread visceral metastases[11] However, even those tumors which remain localized to the end and fail to metastasize sooner or later prove fatal from encroachment on vital structures.



Fig. 171 —Far advanced chordoma of L-4 which has destroyed almost the entire body leaving only the inferior ventral corner (Pantopaque studies were done because of spinal-cord compression.)

As noted, chordoma is so rarely encountered that the experience of any single observer is likely to be limited to a few cases. Considerable interest has been evinced, however in these extraordinary neoplasms, and surveys of more than 100 cases culled from the literature have been made by Mabrey and more recently by Gentil and Coley among others. These are useful for historical background

and clinical orientation particularly From such compilations, one gathers that, while the neoplasm may sometimes appear in infancy or childhood, it is encountered most often in later adult life. The symptoms produced by any particular chordoma depend naturally upon its localization and the direction of its spread. In the basi-cranial region, of course, these relate to manifestations of increased intracranial pressure associated with an expanding lesion in the posterior fossa. With involvement of the vertebral column more caudally one encounters manifestations



Fig 172—Photograph (reduced) of the surgically excised tumor mass in the case of the chordoma of the coccyx illustrated in Fig 170 The specimen represents the extra-osseous extension of the neoplasm, and postoperative roentgenograms showed that relatively little of the involved sacrococcygeal bone was removed. The tumor tissue presented a gelatinous appearance, modified by surgically induced hemorrhage in places. (Courtesy of Dr K F Ernst, Letterman General Hospital, San Francisco.)

of pressure on the spinal cord and its nerve roots (severe pain, paraplegia, incontinence, etc.) The sacrococcygeal tumors in particular which have attained appreciable size and invaded the pelvic structures, may in addition infiltrate and compress the rectum and the urinary bladder giving rise oftentimes to intestinal obstruction, hemorrhage, urinary difficulty and other serious complications.

Roentgenographically chordoma, in the sacrococcygeal region at least, appears as an expanded, rarefied destructive lesion, which is said also to present some evidence of calcification. While this roentgen picture may suggest chordoma to

one who is alert to the possibility it is hardly conclusive in itself and definitive diagnosis must await pathologic examination of an adequate sample of tumor tissue. In this connection, Gentil and Coley, in their report of 7 cases of chordoma have stressed the diagnostic value of needle aspiration biopsy to obviate surgical exposure of the neoplasm.

The pathologic data contained in the relevant articles in the literature relate mainly to microscopic details, but one gathers that the tumor tissue in most pertinent specimens is essentially solid in the gross, although the bulkier tumors may exhibit



Fig 173.—*A* and *B* Photographs (reduced) of another surgically extirpated, bulky mass of chordoma showing the gelatinous appearance also illustrated in Fig 172. (Courtesy of Dr Lauren V Ackerman St Louis)

areas of cystic softening as well as foci of hemorrhage and necrosis. If the neoplasm is not too far advanced nor modified by previous surgical intervention, one may find, further that it is invested by a fibrous capsule and presents a lobulated or bossed surface. What is more significant is that on section it is likely to present a distinctly mucinous or gelatinous character although this feature appears more pronounced in some specimens than in others.

The key to an understanding of the peculiar cytology of chordomas is afforded by information relating to the development of notochordal tissue in the early fetus. Embryologically the notochord, which represents the primitive axial skeleton common to all vertebrates and the forerunner of the cartilage anlage of the vertebral column, appears to be intimately associated in its development with both ectodermal and mesodermal tissues. This consideration, according to Robbins, is significantly reflected in the cytology of chordomas in general. Thus, in any given instance, the tumor may be composed of epithelial like structures or, on the other hand, may closely resemble spindle-cell sarcoma, and frequently both types of cell growth may be observed in the same neoplasm. To be sure, the degree of differen-



Fig 174.—*A* Photograph of a successfully resected chordoma (viewed on its ventral aspect) which had destroyed much of the coccyx and extended into the distal sacral segment (see text for details of this case) *B* Roentgenogram of the surgical specimen illustrated in *A*

tiation, the rapidity of growth and the extent of anaplasia are also factors influencing the cytology of any particular chordoma. Thus, at one extreme, one may observe well-differentiated chordomas containing regular cavities lined by cuboidal epithelium, closely resembling the primitive notochordal tube, and at the other distinctly anaplastic chordomas whose recognition as such may occasion considerable difficulty In most instances, one is likely to observe cords, lobules, or sheets of unusual syncytial cells resembling epithelial cells, separated by matrix containing an abundance of mucin Great emphasis in the matter of specific diagnosis has been placed upon this mucinous intercellular matrix within which the tumor cell aggregates are dispersed, and even more so upon the presence of peculiar large, distended, and vacuolated tumor cells commonly designated as "physallipherous" cells.

It remains to point out two obvious pitfalls in the matter of differential diagnosis. First, in regard to chordomas presenting relatively sparse tumor cells scattered within a distinctly mucinous stroma, a diagnosis of colloid carcinoma (of the rectum) may sometimes be entertained by the unwary who have not taken cognizance of the existence of a large destructive lesion in the sacrum and coccyx. Second, in regard to chordomas whose matrix may acquire a chondroid appearance in places, reminiscent of intervertebral disc tissue, and its cells a rounded contour, the pathologist's impression may be that of chondrosarcoma. Adequate sampling of the available tumor tissue, however, should clearly resolve this difficulty.

In regard to therapy, the consensus of opinion is to the effect that irradiation is not likely to bring about any appreciable regression of the tumor, except perhaps in children,[3] and should be reserved for palliation in far-advanced cases. On the other hand, complete surgical extirpation is usually not feasible because of the location of the neoplasm. In the case of sacrococcygeal chordomas, the sacrum is already more or less extensively involved by the time the presence of the tumor is recognized. One is therefore confronted by a situation involving a choice between two unsatisfactory alternatives. Nevertheless, most observers are agreed that surgical removal of as much of the tumor as possible should be attempted, since even partial resection, repeated when necessary, may result in relief of pain and disability from pressure, and may likewise appreciably prolong life expectancy. As noted, however, the ultimate prognosis is doleful, since sooner or later the tumor proves fatal from the effects of encroachment upon vital structures, although this eventuality may sometimes be delayed several or many years.

For chordomas developing in the coccyx (or even involving the distal sacral segments, as well), early recognition and consideration of radical block excision with a view to clearance are of paramount importance. That the situation is not altogether hopeless is evidenced by the outcome in a patient who was operated on at our hospital in whom the tumor was still well delimited, although it had already substantially destroyed the coccyx and was encroaching upon the sacrum. In this instance meticulous block excision extending through the distal sacral segment apparently effected a cure: at all events, the patient is well over 5 years later, presents no indication whatsoever of local recurrence, and has surprisingly little residual disability (Fig. 174). Another encouraging case in point is that reported by Birrell in which, following excision of a small coccygeal chordoma, there was no recurrence after 9 years' observation.

In the management of chordomas that are no longer amendable to successful treatment by surgery, cognizance should be taken of the claim of Friedman that the result of high voltage irradiation is substantially better than can be obtained by conventional technics.

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XXII

So-Called Adamantinoma of Limb Bones

This discussion, as indicated, deals primarily with so-called adamantinoma as it appears in long bones, notably the tibia, though not exclusively in that site. It will not concern itself with the clinical and pathologic features of adamantinomas as they appear in jawbones, especially the mandible, since these are well known and are discussed in detail in special treatises on oral and dental pathology[13] On the whole, adamantinomas of jawbones are slowly growing and locally invasive neoplasms, although a few may eventually spread to the lungs, while an exceptional one may pursue a rapid or even fulminant course. Through the courtesy of Dr A. G Foord I had occasion to observe material from a case of an unusual, highly malignant adamantinoma of a mandible occurring in a young man 20 years of age, which was so extensively invasive and prone to metastasize as to prove fatal, in spite of vigorous and prompt treatment, within 3 months of the onset of symptoms (Fig 175) It may be noted further that still another less common site of involvement by adamantinoma is the base of the skull in relation to the craniopharyngeal pouch and, as is well known, a certain number of hypophyseal duct tumors (Rathke's pouch tumor craniopharyngioma) may contain adamantine epithelium.

So-called adamantinoma of limb bones is one of the rarer tumors of bone and some 36 cases, more or less, have been recorded since the paper in 1913 by Fischer who is generally credited with the first account of primary adamantinoma of the tibia. The precise number is not important, since undoubtedly many instances go unpublished. The reported cases have all been encountered in the tibia, with the notable exception of one in an ulna described by Anderson and Saunders. In this connection, it is pertinent to note also that I have observed material from an unusual locally recurrent tumor in a radius which I interpreted as an instance of so-called adamantinoma. The cytologic appearance of the neoplasm was appreciably *modified by previous surgical treatment, but the resemblance* to comparable neoplasms that arise in the tibia was still clearly discernible. This case has never been published to my knowledge.

In regard to its pathogenesis, so-called adamantinoma of limb bones represents a curious and intriguing tumor and one wonders naturally how a neoplasm composed supposedly of adamantine epithelium comes to develop in the tibia, unless, as some wag has suggested, the fetus doubles up in utero and bites itself in the leg! One plausible theory is that the tumor in question is derived from deep-seated, aberrant or misplaced embryonal rests of epidermoid epithelium which are stimulated to growth in later life by an injury or by factors unknown. This explanation would account for the fact that some tumors in point have more than suggestive resemblance cytologically in part or substantially throughout, to basal-cell tumors, hence the qualification of so-called adamantinoma. It is in harmony also with the apparently significant fact that the only limb bones in which this tumor has been observed (thus far at least) are those which come in close proximity to the skin namely the tibia and the forearm bones, the ulna and radius.

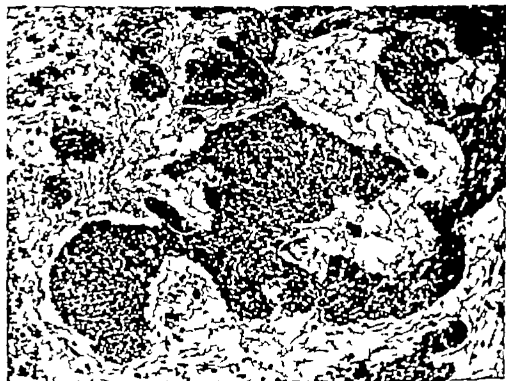


Fig. 173 —Photomicrograph of a representative field of an unusually aggressive, metastasizing adamantinoma of a mandible, which proved rapidly fatal (×100)

Another alternative explanation advanced by Ryrie and accepted by Dockerty and Meyerding, among others, postulates the transplantation of epidermoid cell nests into the site at which tumor subsequently develops, as a result of trauma. This theory however would hardly explain satisfactorily the initial development of the tumor within the interior of the affected bone particularly in patients who had not previously sustained a fracture. I have had the opportunity of examining a resected specimen of a so-called adamantinoma of a tibia in an early stage of

its evolution The intact tumor which was circumscribed ovoid-shaped and measured no more than 2 cm. in its greatest dimension was eccentrically placed within the medullary cavity To be sure, it had eroded the cortex endosteally but otherwise the overlying cortex and its periosteal covering were intact The amputation specimen illustrated by Coley likewise clearly demonstrates the initial central or medullary localization of the tumor Furthermore if the tumor has its essential basis in trauma as suggested one may justifiably inquire why it should be so rare when injuries to the leg and particularly fractures of the tibia are so common.



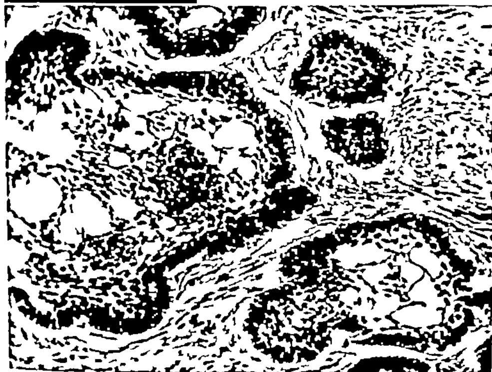


Fig 1 6—*A* Roentgenogram of a resected adamantinoma of a mandible. *B* Photomicrograph of another adamantinoma of a mandible which was locally invasive and recurred twice after unsuccessful attempts at surgical extirpation The tumor proved fatal after 5 years of treatment as a result of exsanguination presumably due to erosion of a large blood vessel. No metastases were found at autopsy (×200.)

Be that as it may most observers in this country seem to favor the theory of origin from epidermoid or basal-cell inclusions (or both) irrespective of whether or not a factor of trauma is also invoked Among pathologists in the British Commonwealth, Willis has unequivocally endorsed this stand, whereas Hicks and Lederer and Sinclair have advanced the interesting suggestion that "adamantinoma" of the tibia is really synovial sarcoma in disguise. Still another intriguing hypothesis was recently ventured by Changus, Speed, and Stewart to the effect that so-called adamantinomas of long bones have a vascular genesis and actually represent malignant angioblastomas. It occurs to me that this interpretation based upon histochemical studies fails, from a broader point of view to explain why the tumors in question have been encountered only in the tibia (or at any rate, only in superficial limb bones) or why certain of them contain what appear to be squamous nests exhibiting pearl formation microscopically nor is it in harmony with the fact that their clinical behavior is essentially different from that of unequivocal malignant tumors of vascular origin arising in bone (as described in Chapter 12) which are, as a rule, highly aggressive, notoriously bad actors. Altogether it is my impression at this time that one should keep an open mind about the whole question of histogenesis.

Clinically, the tumor develops insidiously and slowly often over a period of years, and manifests a tendency to gradual but progressive local invasion. From some of the recorded cases it is known also that the tumor is capable at times of extension to regional lymph nodes and even of metastasis to the lungs, and one must be alert to these possibilities. In a considerable number of the cases reported, though by no means all, the past history contains some reference to previous injury to the affected site, often an old healed fracture. The usual difficulties calling attention eventually to the presence of the lesion are pain and some swelling and induration of the affected limb, and occasionally pathologic fracture.

Roentgenographically the tumor appears as a smaller or larger finely trabeculated, expanded rarefied lesion, with a well-defined peripheral outline. The overlying cortex is likely to be attenuated and somewhat expanded but is usually not broken through unless there has been previous surgical intervention. Also, as a rule, one observes little if any spontaneous periosteal new bone reaction. If the tumor has been allowed to progress for a number of years, it may attain large size and come to involve a substantial or major part of the shaft of the affected bone Thus, in the specimen described by Halpert and Dohn, the tumor (in a tibia) measured fully 15 cm. in length, and in that reported by Anderson and Saunders, it came eventually to involve as much as two thirds of the shaft (of an ulna) In such large specimens, one finds the shaft of the affected bone appreciably widened and otherwise deformed. Also by the time amputation is resorted to the tumor may already have extended through the cortex into the contiguous soft parts, sometimes spontaneously but more often, as a result of fracture or previous surgery Altogether the slow evolution of the lesion its peculiar localization in the tibia (with few exceptions) and its roentgen picture, which is not calculated to suggest any other neoplasm in particular should point to the possibility of adamantinoma Nevertheless, most cases are not recognized prior to biopsy

and some even after biopsy is performed because of unfamiliarity with the tumor or because the possibility is not considered owing to its rarity

On examination of biopsy material or of an amputation specimen one observes that the tumor tissue if its appearance has not been altered by previous treatment, is gray or gray white and is rather firm in consistency Its histologic appearance may vary from specimen to specimen, and even in different fields of the same specimen. In places, one may observe a suggestive glandular pattern reminiscent of certain adamantinomas of the mandible, which may be mistaken for metastatic adenocarcinoma by the unwary (Fig 177) In other fields, as noted, one may be impressed by the resemblance to a basal-cell tumor growing in strands or nests



Fig. 177.—Photomicrograph of a representative field of a so-called adamantinoma of a tibia (one of the two cases reported by Wolfort and Sloane, which eventually came to amputation after unsuccessful attempts at local resection and reconstruction.) (×100)

which may exhibit pseudoglandular or cystic change. In still other fields of one specimen or another the tumor may appear epidermoid and exhibit suggestive pearl formation, so that it may be mistaken for squamous-cell epithelioma invading bone, if one has not inquired into the pertinent clinical findings.

In regard to treatment, it should be emphasized that the tumor tissue is highly radioresistant and that surgical excision or ablation affords the only means of cure. If an adamantinoma of a limb bone is approached for the first time and is still relatively small and localized one may be justified in advocating block excision of the tumor focus in an attempt to salvage the limb On the other hand if this

procedure should prove unsuccessful or if when the tumor is explored, it is found to have already invaded too widely to make resection feasible, amputation should be resorted to without undue delay Repeated experience with such cases has clearly demonstrated the futility of compromising with the necessity for radical surgery This point has been stressed by Anderson and Saunders, Dockerty and Meyerding, and Halpert and Dohn, among others. Also in the two cases reported by Wolfort and Sloane which I had occasion to review repeated attempts at local excision of the tumor and reconstruction proved unsuccessful and led eventually to amputation for recurrent tumor after the patients had been subjected to several years of needless disability The feeling of complacency once held in regard to these tumors and the leisurely approach it engendered are no longer justified As noted, clinical follow up data are slowly accumulating to indicate that they not only tend regularly to recur (locally) but may also extend to regional lymph nodes and even metastasize to the lungs. The importance of prompt ablation of the affected extremity once the diagnosis is clearly established, is thus heavily underscored.

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XXIII

Carcinoma Metastatic to the Skeleton

Metastatic carcinoma is by far the most common malignant bone tumor and, as such, must weigh heavily in any consideration of differential diagnosis. The pertinent literature that has developed through the years is too voluminous to review here—literally thousands of papers have been written on the subject—nor would it be particularly profitable to do so except to comment on some significant recent advances in therapy notably hormonal therapy for prostatic and breast cancer and the use of radioactive iodine for selected cases of thyroid cancer I will be content to record certain impressions, gleaned empirically for the most part relating to the recognition and treatment of metastatic foci in the skeleton, particularly from such primary sites as the breast, prostate, lung kidney and thyroid among others.

It appears to be valid and useful to distinguish between carcinoma involving contiguous bones by direct extension and that spreading by hematogenous dissemination. As rather well-known instances of the former one may cite erosion of the facial bones or calvarium by burrowing squamous or basi squamous carcinoma of the skin invasion of the maxilla or mandible by squamous-cell carcinoma of the mouth tongue and occasionally the lip erosion of the maxillary ethmoid and nasal bones as well as of the base of the skull by tumors of the nasopharynx invasion and partial destruction of ribs and chest wall by direct extension of carcinoma originating in the lung or breast invasion and collapse of cervical vertebrae by Pancoast tumor extension of advanced bladder carcinoma into the pubic bones and also extension of advanced rectal carcinoma to the pelvic bones or sacrum and coccyx.

The incidence of metastasis to the skeleton by carcinoma in general, from whatever primary site is probably greatly underestimated. Only a limited number of such foci manifest themselves clinically through the development of severe pain a palpable tumor mass, pathologic fracture (usually of a rib or a long bone) or neurologic manifestations of compression of the spinal cord or its nerve roots as a



Fig 178.—Roentgenogram of a resected mandible showing moth-eaten rarefaction and destruction reflecting invasion by squamous-cell carcinoma originating in the floor of the mouth.

Fig. 179.—*A* Roentgenogram showing widespread lytic defects and a number of pathologic fractures resulting from skeletal metastasis of a breast carcinoma. *B* Calvarium from another case of breast carcinoma showing multiple lytic defects representing metastases.

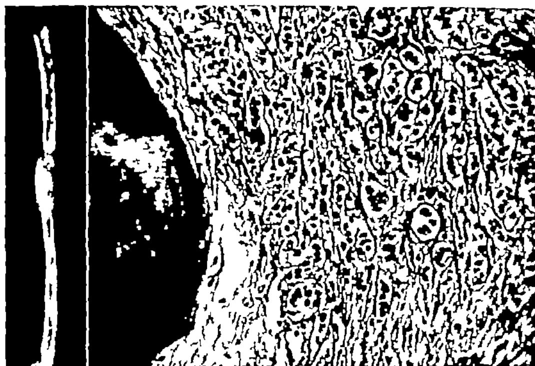
result of vertebral column involvement. Many more give rise to only a vague awareness of their presence or are entirely occult. If one resorts to roentgen skeletal survey many additional carcinoma foci may come to light, but one must recognize that roentgen examination alone has inherent limitations also and does not necessarily begin to indicate the full extent of skeletal involvement.



A B

Fig. 180.—*A* Roentgenogram from still another instance of carcinoma of the breast with wide spread skeletal metastases showing a lytic focus in the upper femur and a sclerosing one in the adjacent innominate bone. *B* A segment of the spine from the same subject showing compression of the vertebral bodies and the presence of both osteolytic and osteoplastic metastases

To what extent the spread of carcinoma to the skeleton is revealed by autopsy depends obviously upon the thoroughness with which the bones are examined grossly and microscopically It is unfortunately true, for one reason or another that the skeleton is regarded by many pathologists as a sacred cow and its examination is usually limited to taking a slice of the ventral aspect of a few lumbar vertebral bodies occasionally supplemented by inspection of the sternum or of one or two ribs. It is significant, therefore, to point out that in a recent survey of the metastases in carcinoma based upon an analysis of 1 000 autopsied cases, Abrams, Spiro and Goldstein found the incidence of widespread metastases includ



A *B*

Fig 181—*A* Roentgenogram of a rib from the case illustrated in Fig 180 showing multiple lytic defects including one which has destroyed a short segment of the rib *B* Photomicrograph of a biopsy specimen of a lytic rib lesion in a comparable case, showing replacement of the spongy bone and marrow by undifferentiated scirrhous carcinoma. (×200)



Fig 182—Photomicrograph of a focus of sclerosing metastatic adenocarcinoma The primary tumor was in the cecum (×125)

ing those in the skeleton to be substantially higher than the literature would lead one to believe. Their findings reflect the meticulous care and thoroughness in the performance of autopsies which are traditional at the Montefiore Hospital (New York City). Specifically, in their large series of cancer patients, 27 per cent of the entire group showed skeletal metastases. Their analysis also revealed that over two-thirds of the breast carcinomas, approximately one-third of the lung tumors, and one-fourth of the renal tumors had spread to one or more bones. It



Fig. 103 — *A* Roentgenogram from a case of prostatic carcinoma with widespread sclerosing metastases in the spine and pelvis. This patient had received the benefit of estrogen therapy but succumbed after several years from the effects of visceral metastasis. *B* Photomicrograph of a needle aspiration biopsy of an involved lumbar vertebral body in another instance of prostatic carcinoma. (×100)

showed further that carcinoma in still other sites not ordinarily thought of as spreading to the skeleton had nevertheless done so in an appreciable number of instances (e.g., pancreas 13 per cent, rectum 13 per cent, stomach 11 per cent, colon 9 per cent, ovary 9 per cent). In the same connection it is pertinent also to point out, as is well known, that thyroid carcinoma often metastasizes to one, several or many bones and that more than half of all prostatic carcinomas likewise spread to the skeleton, particularly to the pelvis and lumbar vertebral column.

What is perhaps not generally appreciated is that neoplasms of the testis (be they seminomas, embryonal carcinomas or teratocarcinomas) also metastasize not infrequently to the skeleton, particularly to the spine. Malignant melanoma may likewise do so especially in its late phase of widespread dissemination, and it is interesting to note in this connection that some of the bone metastases may be heavily pigmented while others may be virtually non-pigmented, as observed for instance in adjacent bodies of a vertebral column specimen. Even malignant carcinoid tumors



Fig. 184.—*A* and *B* Diffuse osteosclerosis attributable to widespread skeletal metastasis from a small gastric carcinoma the presence of which was not recognized until autopsy was performed The provisional clinical impression was marble bone disease or possibly endemic fluorosis.

may sometimes spread to the skeleton and without detailing further specific instances, suffice it to state that on occasion virtually every malignant neoplasm may do so, some more often than others.

It is pertinent also to comment briefly upon the matter of localization in one part of the skeleton or another The predilection of carcinoma metastases for the innominate bones, the vertebral column, and the ribs is well known. It is not generally appreciated, perhaps that the calvarium also is not infrequently involved

(e.g., by thyroid carcinoma) and that sometimes it may be so riddled by osteolytic defects as to simulate the picture usually held to be typical of multiple myeloma (Fig 186) Also if one is willing to search for it involvement of long limb bones and of the bones of the shoulder girdle is not infrequently observed As for the remainder of the skeleton it is generally held that it is distinctly unusual to find skeletal metastases below the elbows and knees, and yet, such are the vagaries of

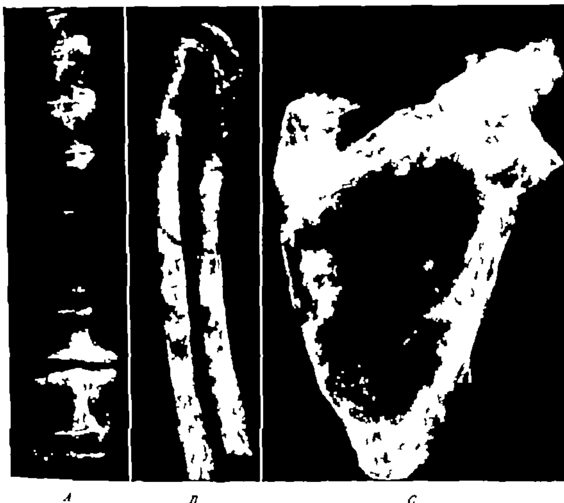


Fig 183—A B and C Roentgenograms from an autopsied case of prostatic carcinoma showing punched-out lytic defects (in the scapula) as well as the usual osteoplastic metastases (in the vertebral column and ribs.)

carcinoma metastasis that Dr G J Hummer of Los Angeles has had occasion to observe an instance of carcinoma of the colon which metastasized to the bones of both hands and feet.

The roentgen picture produced by *carcinoma foci in the skeleton is much too* varied to permit formulation of any integrated comprehensive description. By the same token, it is difficult to surmise except in a few special instances (e.g., prostatic carcinoma and sometimes renal or thyroid carcinoma[11, 12]) what the primary site of

any given carcinoma may be from the roentgen appearance of its skeletal metastases. In fact, it may be difficult in any specific instance to distinguish clearly a single focus of metastatic carcinoma from a primary malignant tumor of bone, e.g., a solitary myeloma or on occasion even osteogenic sarcoma. All that one can say with any assurance in such cases is that one is dealing with a malignant neoplasm, and that biopsy is indicated for definitive diagnosis. For such lesions suspected of being foci of metastatic carcinoma, aspiration biopsy has been advocated rather than open biopsy and Coley has claimed a high degree of accuracy for this procedure (90 of 107 cases or 84 per cent) Further as is well known, multiple punched-out



Fig 186 —Calvarium from the case of prostatic cancer illustrated in Fig. 185 showing wide spread, well-defined lytic defects indistinguishable from those commonly encountered in multiple myeloma.

defects of metastatic carcinoma must be distinguished particularly from those of multiple myeloma, and this differentiation is not invariably simple, at least from the roentgenograms alone. Also as has been pointed out elsewhere, an unrecognized small primary carcinoma (e.g., in a small-order branch bronchus or in the gastric mucosa) may sometimes give rise to widespread skeletal metastases, and the latter may then be misinterpreted as lesions of Ewing's sarcoma.

It is customary in describing carcinoma metastases in the skeleton to distinguish between those which are essentially destructive (osteolytic) and those which pro-



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It is customary in describing carcinoma metastases in the skeleton to distinguish between those which are essentially destructive (osteolytic) and those which pro-

voke significant reactive osteosclerosis (osteoplastic) Actually the great majority of carcinoma metastases in bone are lytic in their effect, and only in dealing with prostatic carcinoma does one consistently observe osteosclerotic reaction although breast and urinary bladder cancers may have this effect and, occasionally tumors arising in other primary sites Moreover this distinction is a relative one in the sense that a breast cancer for instance may give rise to osteolytic metastases in some bones and osteoplastic metastases in other bones in the same case (Fig 180)

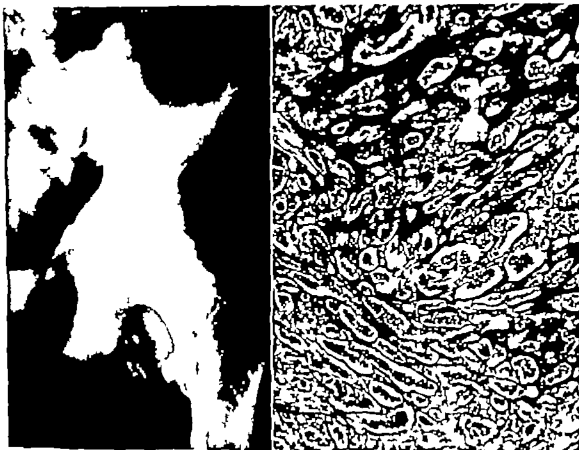


Fig. 187 – 4 Another instance of carcinoma of the prostate with osteoplastic metastases in the spine and innominate bones. *B* Photomicrograph of a field from a sclerosing skeletal metastasis showing scirrhous reaction and early osseous metaplasia of the connective tissue stroma (×100)

Some consideration should be given to certain blood chemical findings as they relate to diagnosis and particularly to significant alterations in the values of serum calcium, phosphorus, and phosphatase activity The serum calcium level may remain within normal limits even in the face of obvious skeletal metastases, although not infrequently it is slightly elevated and occasionally especially when the vertebral column is undergoing rapid demineralization, it may be very significantly increased to 16 mg or more In such cases, as in comparable instances of multiple

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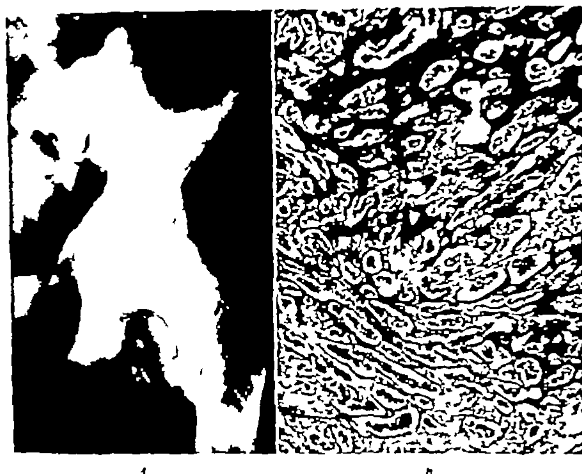


Fig 186.—Cal arium from the case of prostatic cancer illustrated in Fig 185 showing wide spread, well-defined lytic defects indistinguishable from those commonly encountered in multiple myeloma.

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A *B*

Fig 18[illegible]—*A* Another instance of carcinoma of the prostate with osteoplastic metastases in the spine and innominate bones. *B* Photomicrograph of a field from a sclerosing skeletal metastasis showing scirrhous reaction and early osseous metaplasia of the connective tissue stroma. (×100)

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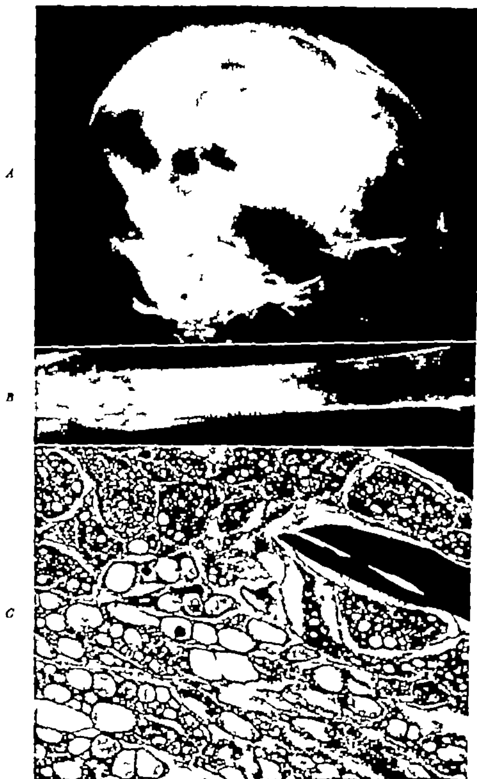


Fig. 168.—*A* Roentgenogram from a case of thyroid carcinoma showing striking, large, circumscribed lytic metastases in the calvarium. *B* Comparable lesions in the shaft of a femur. (Additional metastatic foci were present in other bones also.) *C* Photomicrograph of one of the skeletal metastases showing the formation of well-differentiated colloid containing thyroid acini. It is in instances such as this that one is rather likely to observe the uptake of radioactive iodine. (×75)

myeloma, one may observe conspicuous calcium deposition in the renal pelvis and tubules, the lungs, and sometimes the gastrointestinal tract as well. The serum phosphorus level is not likely to be significantly increased unless there has been concomitant renal damage and associated phosphate retention. As for the serum alkaline phosphatase activity, slight or appreciable increases are not infrequently observed, particularly if pathologic fractures have occurred and if the skeletal metastases have provoked bone formation. One must be wary, however, of ascribing

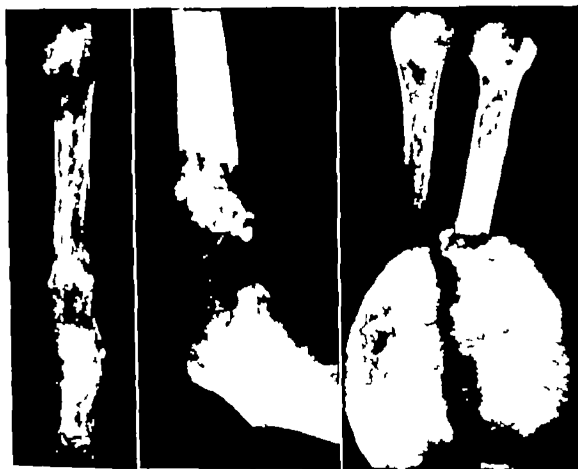


Fig. 189.—*A*, *B* and *C*. Three instances of renal carcinoma (hypernephroma) metastatic to the humerus. *A* and *C* represent amputation specimens.

such increased values to skeletal metastases alone, unless one can rule out the possibility of liver metastases. In the presence of well-established, osteoplastic metastases, particularly from prostatic cancer, appreciable though not necessarily dramatic elevations of serum alkaline phosphatase activity are to be expected, and in such cases, values of 10 to 20 or more Bodansky units are not unusual. In cases also of prostatic carcinoma invading the surrounding soft tissues and metastasizing to the spine and pelvis, significant elevation of the serum acid phosphatase level is

A



C. B

Fig. 190.—*A*, *B* and *C*. Another instance in which biopsy of a metastatic focus in a humerus (*B* and *C*) led to the discovery of a hypernephroma of a kidney. Nephrectomy was followed by ablation of the involved upper limb in an attempt to obtain a cure (roentgen skeletal survey revealed no other discernible metastatic lesions). It is interesting to note that this patient had a remission for as long as 8 years before he manifested another tumor focus in a femur.

commonly observed although this does not occur in every instance while the extent of the elevation when present varies from case to case With clinical remission following estrogen therapy or castration one may anticipate a prompt and sharp fall in the serum acid phosphatase value although the alkaline phosphatase level may rise for a time as a reflection of tumor necrosis and accelerated calcification and ossification of osseous metastases.[7]

In regard to therapy also attention should be directed to the well known observation that in metastases from breast carcinoma roentgen sterilization and steroid therapy may in some instances at least bring about temporary regression

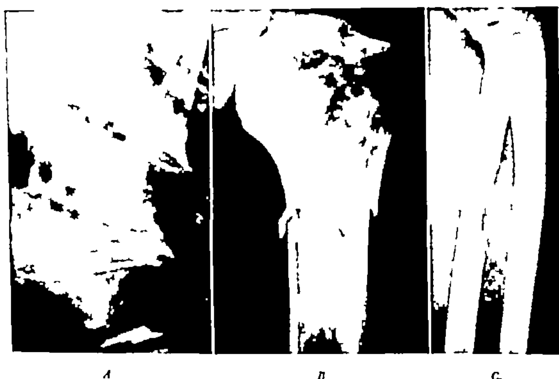
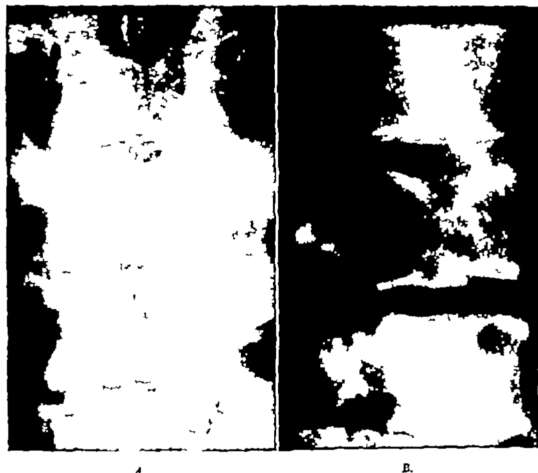


Fig 191 —Three instances showing more unusual skeletal metastases of carcinomas originating in the respiratory tract *A* In the larynx (collapsed and wedged vertebra) *B* In the trachea (pathologic fracture of a humerus) *C* In the lung (destructive tumor focus in the shaft of a radius as the initial clinical manifestation)

of skeletal metastases, although the metastases elsewhere are not likely to be significantly influenced For a detailed account of the beneficial effects of intensive therapy with estrogens and androgens as well as its limitations and complications, the reader is referred to a number of pertinent articles listed in the references at the end of the chapter Huggins and his associates have demonstrated that adrenalectomy may cause significant regression in selected cases of human mammary cancer of small glandular functioning type (associated with abundant urinary excretion of estrogen) but this appears to be of greater theoretical than practical importance. Specific mention should also be made of the demonstrated value of radioactive iodine

in the prolonged palliation of selected cases of thyroid cancer with skeletal metastases, particularly those which are of the nature of functioning, colloid-producing adenocarcinoma and, as such, exhibit the capacity to pick up and retain the radioactive substance.[4, 18]

The question of surgical eradication of an ostensibly solitary skeletal metastasis as a curative measure seldom arises, except in occasional instances of renal carcinoma (hypernephroma) This particular neoplasm may exhibit a curious tendency to



A B.

Fig 192.—Two additional instances showing unusual metastases in the spine. *A* A single sclerosed body reflecting metastasis from a carcinoma of the urinary bladder *B* Pathologic fracture through a vertebra in a case of cancer of the pancreas. Roentgenograms taken 3 weeks earlier revealed no discernible lesion at the site indicated.

spread to a single bone, particularly the humerus, at least in so far as one can ascertain from roentgen skeletal survey and moreover it faithfully reproduces the cytology of the primary clear-cell carcinoma in its skeletal metastasis, so that it may become feasible to undertake nephrectomy followed by surgical ablation of the metastatic skeletal focus I have observed several instances in which this was done in an attempt to obtain a cure in one of them a remission for as long as 8 years was obtained, but then other skeletal metastases appeared (see Fig 190)

As for the rest, x-ray irradiation may be resorted to for palliation of skeletal metastases. One must bear in mind, however, that the dosage should not be pushed to the point where it induces radiation necrosis or enhances the likelihood of pathologic fracture and that the results, while distinctly worth-while in many instances, are on the whole unpredictable.

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XXIV

Tumors of Periosteal Origin

Inasmuch as the periosteal covering of bones may be regarded logically as an integral part of the skeleton, this chapter has been added for the sake of completeness and to enhance the usefulness of the book. It includes the material presented in my paper[18] in *Cancer* in 1955 with some additions and changes intended to bring the discussion up to date Prior to this survey there appears to have been no comprehensive discussion on record of tumors developing within periosteal connective tissue, although there were some reports of unusual cases or of small groups of cases demonstrating the characteristic features of some particular periosteal tumor or other These comparatively uncommon neoplasms constitute a group unto themselves, and their pathologic traits and clinical behavior must be determined empirically rather than inferred by analogy The behavior of a periosteal fibrosarcoma, for example cannot be predicted from that of a central fibrosarcoma of bone. It is only in recent years that the field has been explored to any significant degree, and there is still much to be ascertained, as will be indicated presently

The main purpose of this chapter is to survey and integrate the limited information now available and to highlight certain practical problems in diagnosis and treatment that require further clarification. In particular the significance of cartilaginous and/or osseous metaplasia of periosteal connective tissue leading to the formation of juxtacortical tumorlike masses and the incidence of eventual malignant change in such lesions will be considered. Specific reference will also be made to periosteal fibroma, neurofibroma, lipoma, and chondroma as the major benign tumors in point, and to fibrosarcoma, chondrosarcoma, and osteogenic sarcoma as the malignant ones. It is altogether probable that on rare occasions neoplasms of other types may arise from the periosteum, but too little is known about their incidence for them to serve as a basis for discussion.

Mention should also be made in passing of pseudotumors on the surface of affected bones induced by penetrating thorns,[20] for example reflecting unsuspected fracture callus, or developing through innocuous localized periosteal ossification with-

out apparent cause Such lesions are not infrequently explored for biopsy because of a roentgenographic suspicion of sarcoma especially osteogenic sarcoma but are otherwise not relevant here

Benign Tumors

Periosteal Fibroma.—On occasion one may observe a comparatively small circumscribed benign fibrous growth on the surface of a large limb bone ostensibly arising in its periosteal covering Four pertinent instances were reported by Kimmelstiel and Rapp in 1951 under the title of *Cortical Defect Due to Periosteal Desmoids* All of these remarkably enough were encountered on the lower femur in the

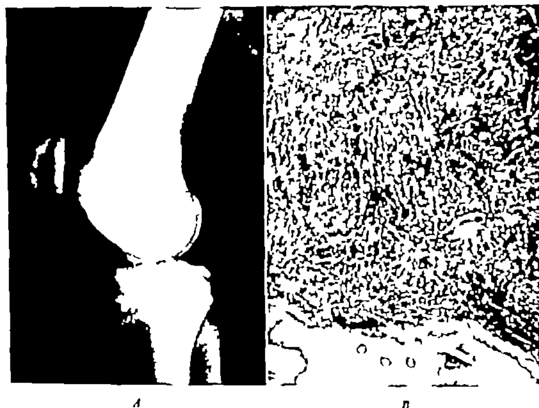


Fig 193 *A* Roentgenogram of a periosteal fibroma on the posterior aspect of the lower femur that has eroded a sclerotized shallow trough in the cortical bone *B* Photomicrograph of a representative field of the periosteal fibroma illustrated in Fig 193 *A* (×58) (From Lichtenstein, L Tumors of Periosteal Origin Cancer 8: 1060 1955)

supracondylar region. It seems noteworthy also that their patients were all young males between the ages of 8 and 20 years. Although Kimmelstiel and Rapp favored the interpretation of localized periosteal fibrosis or fibroplasia their observations seem more indicative of a benign fibroblastic tumor (fibroma) because of the circumscribed character and limited size of the lesion as well as its relative acellularity In any event it should be clearly distinguished from the larger poorly defined and more cellular fibrosarcomas of the periosteum which will be considered

farther on. Another relevant report is that of Marek (1955) dealing with two periosteal fibromas, both in boys, situated in the lower metaphysis of the femur and the tibia respectively for which surgery was performed.

Several years ago I had occasion to observe a comparable instance (in a 15-year-old boy) situated on the lower shaft of a femur posteriorly in the supracondylar area, a little above the attachment of the capsule of the knee joint (Fig 193 *A*) The lesion was discovered on roentgen-ray examination after an injury and had evidently been present for some time, for it had eroded a sclerotized somewhat scalloped, shallow trough in the underlying cortical bone in much the same way that a periosteal chondroma does (Fig 194 *A*) Despite this feature that clearly pointed to the benign character of the lesion, the initial radiologic impression was that of a periosteal sarcoma. Fortunately conservative surgical excision was done and examination of the available sections (Fig 193 *B*) showed a mature fibrocytic growth manifesting no indication of significant recent activity Incidentally its random content of giant cells (mainly within or in proximity to blood channels) gave this particular tumor a superficial resemblance to non-osteogenic fibroma of bone (which of course, is a subcortical intramedullary lesion) I have also observed a very similar instance in an 8-year-old boy in which the lesion was likewise detected roentgenographically following an injury

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It appears further from the observations of Weber that, on occasion, periosteal neurofibroma may come to involve a major part of the shaft of a limb bone and result in rather striking diffuse periosteal thickening as well as appreciable thickening and irregularity of the adjacent cortical bone. It should also be noted that if malignant change ensues in von Recklinghausen's neurofibromatosis, as it commonly does, such Schwannian tumors may extensively erode and invade contiguous bones, e.g., multiple bodies of the vertebral column.

Periosteal Chondroma.—In 1952, I, in collaboration with J. E. Hall,[9] drew attention to a distinctive benign cartilage tumor that was designated "periosteal chondroma." This paper stressed the salient clinical, roentgenographic and pathologic features as observed in 6 instances, 4 of which were encountered on hand or foot bones and 2 in apposition to the shafts of large limb bones. Within the past several years I have observed material from 7 additional cases (4 on phalanges of fingers and 1 each on the shaft of the tibia, the humerus, and the femur, respectively) that have served to substantiate our original impressions. As previously noted,[19] periosteal chondroma is a slowly growing neoplasm of comparatively small size that develops within the periosteal connective tissue and characteristically erodes and induces appreciable sclerosis of the contiguous cortical bone. As such, its roentgenographic appearance has a certain distinctiveness that enables one to recognize the lesion if he is familiar with it and clearly to distinguish it from osteochondroma as well as from solitary enchondroma (Fig. 194 A and B). Two pertinent instances, each of which developed on the calcaneus, were reported recently by Fernberg and Wilber. It is of interest to note that there was a history of intermittent, painful swelling for as long as 8 years in 1 case and 10 years in the other and that in both the correct diagnosis was suspected from roentgen examination prior to surgical extirpation. A number of additional instances in point were also recorded by Jaffe[13] under the head of "juxtacortical chondroma."

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The treatment recommended in most instances is conservative surgical extirpation and curettement of the eroded, sclerotized cortical base. Block excision is feasible if the tumor has involved a long limb bone and is substantially larger than it is on the phalanx of a finger for example. The results of treatment by either method have been uniformly satisfactory The patients covered by our original

report have been followed for several years now and there has been no indication of any tendency to local recurrence following surgical excision.

On the other hand Dr J L. Carr of San Francisco has called my attention to a periosteal chondroma in a 49-year-old man that recurred 3 years after surgical extirpation. The recurrent tumor was somewhat more cellular than the original



Fig 191—*A* Roentgenogram of a periosteal chondroma of the proximal phalanx of a finger of a 5-year-old child At surgery a firm rubbery whitish tumor node was found lodged in the gouged-out cortical defect. *B* Roentgenogram of another periosteal chondroma protruding from the medial aspect of the upper tibia of a 37 year-old woman who had been aware of the growth for 10 years, according to the history In this instance, the tumor shows spotty calcification and is outlined peripherally by a delicate shell of periosteal new bone. *C* Photograph (enlarged) of a periosteal chondroma that was shelled out of a hollow in the cortex of a first metatarsal bone The tumor was adherent to the periosteum and presented a glistening white bosselated surface. *D* A representative field of a periosteal chondroma showing its cytologic details. Although the cartilage-cell nests are more compact than they would be ordinarily in a solitary enchondroma and some of the nuclei are relatively plump these findings should not be interpreted as indications of malignant change. (×175) (From Lichtenstein L., Tumors of Periosteal Origin Cancer 8: 1060 1955)

one but was still apparently circumscribed. At the follow up 2½ years later the patient was in good health and presented no evidence of tumor either at the local site or elsewhere Whether or not the initial tumor was completely removed cannot now be ascertained. In any event, this experience, while it gives one pause, would seem to be the exception that proves the rule.

Periosteal or Parosteal Lipoma.—The specific reference here is to the very occasional finding of a slowly enlarging circumscribed, benign growth of lobulated simple fat developing deep in the soft parts of an extremity in intimate contact with the periosteum of a limb bone. Whether the lipoma under these circumstances actually arises in the periosteum or merely comes in apposition to it may be difficult to determine with assurance in any particular case. It seems noteworthy however that in 2 pertinent instances in children, reported by Bartlett, the lipomas were so adherent to the thickened periosteum of the affected bone (a tibia and a humerus, respectively) as to require sharp dissection for their separation. Such tumors may eventually attain appreciable size. Their presence is reflected roentgenographically by a well-outlined, ovoid, translucent, soft-tissue mass abutting on the contiguous bone usually a long limb bone When fully developed they produce discernible swelling without being especially painful, although they may sometimes cause pressure on nerves in their vicinity Richmond, for example has described a lipoma attached to the periosteum of the neck of a radius that displaced and impaired the function of the posterior interosseous nerve. A comparable instance, though without paralysis, was recorded by Fairbank, to whom we are also indebted for a survey of the older literature dating back to 1868.[2, 34, 28] Among the references mentioned, that of Bland-Sutton in which 14 relevant cases are cited seems particularly noteworthy Altogether these deep-seated periosteal lipomas seem to be distinctly unusual. I have observed only one in my own experience and am not aware of any recorded instance in which malignant change ensued.

Malignant Tumors

In the interest of clarity a sharp distinction must be made at the outset between the malignant tumors that apparently originate in the periosteum and the parosteal soft part tumors (e g fibrosarcoma, liposarcoma malignant Schwannian tumors, and myosarcoma) which in the course of their growth come to erode the adjacent bone and its periosteal covering secondarily These parosteal tumors, while interesting in their own right, are not the subject of the present discussion. This will be concerned rather with the recognition and appropriate treatment of the comparatively unusual instances of periosteal fibrosarcoma, chondrosarcoma, and osteogenic sarcoma, respectively In regard to the latter two neoplasms, particularly the data now available are hardly adequate for any definitive discussion, but it seems worth while to present them nevertheless, if only to stimulate interest in the subject and to provide a framework of reference within which further relevant observations may be charted

Periosteal Fibrosarcoma.—Malignant fibroblastic tumors are occasionally encountered that seem clearly to arise from the periosteal connective tissue and produce a slowly enlarging mass intimately attached to the external surface of the affected bone. When they have attained appreciable size prior to surgical intervention, these periosteal fibrosarcomas may sometimes erode the underlying cortical bone although they do not, as a rule invade the medullary cavity As indicated elsewhere (p 216) Stout has reported 13 pertinent instances, of which 8 developed on

other than large limb bones, notably the scapula, the mandible, and the sacrum and coccyx. He is inclined to regard them as relatively favorable neoplasms (as compared with fibrosarcomas in other sites) inasmuch as metastasis was observed in only one of his 13 cases. The relatively few periosteal fibrosarcomas that I have observed have been tumors of rather low-grade malignancy exhibiting a tendency to relatively slow growth and a disposition to merely local recurrence after incomplete surgical extirpation. Initial radical surgery for such tumors would seem unnecessarily drastic unless they are so situated or so far advanced that the surgeon cannot obtain adequate clearance by more conservative measures.



A B

Fig 193.—*A* Roentgenogram of a localized tumor on the upper shaft of a humerus, which was interpreted cytologically as an early chondrosarcoma. *B* A representative field of the periosteal chondrosarcoma illustrated in Fig 193 *A* The darker strands reflect collagenization of the matrix in places (×210) (From Lichtenstein, L. Tumors of Periosteal Origin Cancer 8. 1060, 1955)

Periosteal Chondrosarcoma.—Malignant periosteal tumors composed entirely of cartilage are comparatively rare although some periosteal osteogenic sarcomas may present conspicuous fields of tumor cartilage. I have observed only one periosteal tumor that could be plausibly interpreted as an early (true) chondrosarcoma. This was a rather small localized growth on the upper shaft of the humerus (of a young adult) which was partially walled off by a shell of periosteal new bone. Its roentgenographic appearance was, in fact reminiscent of periosteal chondroma

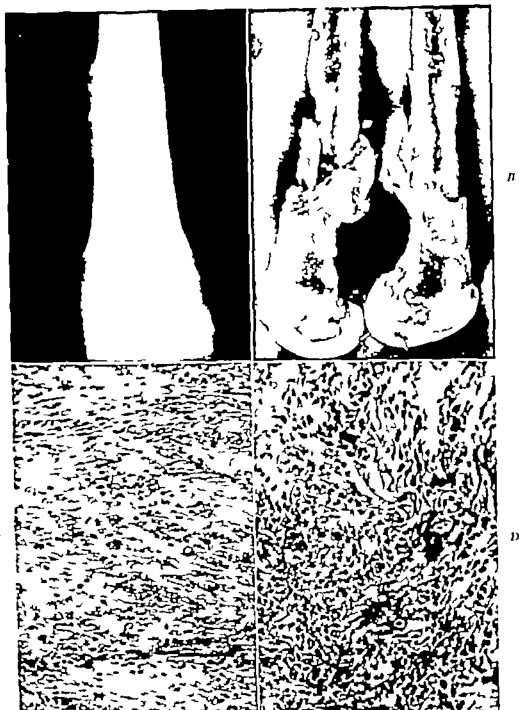


Fig. 196.—*A* Roentgenogram of a tumor on the lower shaft of the femur of an 18-year-old boy which proved to be a periosteal osteogenic sarcoma. *B* Photograph of the recurrent periosteal tumor in the case illustrated in Fig. 196, *A* as seen in the amputation specimen. The medullary cavity of the femur was found to be free of tumor. *C* The appearance of the tumor illustrated in Fig. 195 *A* and *B* as seen in the original biopsy specimen. From this, the impression gained was that of a chondrosarcoma. (×175) *D* A selected field in the amputation specimen indicating that the neoplasm was actually an osteogenic sarcoma. (×200) (From Lichtenstein, L.: Tumors of Periosteal Origin, Cancer 8: 1060, 1955.)

(Fig 195 *A*) although the relative cellularity of the tumor in places (Fig 195 B) and its tendency to invade the contiguous cortical bone favored an impression of low-grade malignancy so that wide block excision was recommended. This was done and at the last follow-up about 1 year later the patient was well clinically and showed no sign of local recurrence.

To emphasize the problem of differentiation between chondrosarcoma and osteogenic sarcoma it may be helpful to cite the following instance of another unusual neoplasm, which developed on the lower shaft of a femur of an 18-year-old boy (Fig 196, *A*) On initial biopsy it was interpreted as a periosteal chondrosarcoma but in subsequent specimens it showed *other features clearly stamping it* as a cartilage-containing osteogenic sarcoma (Fig 196 *C* and *D*) When first explored, this tumor presented as a somewhat nodular rubbery gray mass, 4 by 1.5 cm. sitting on the intact cortex of the femur from which it came away with ease. The available sections of this, as noted showed a dominant picture of rather cellular tumor cartilage undergoing focal calcification and osseous transformation. Examination of the recurrent neoplasm, however revealed, in addition to abundant *cartilage fields of malignant spindle connective tissue, forming osteoid in places.* Following an unsuccessful attempt at wide block excision, infection developed and amputation was resorted to Study of the residual tumor in the amputation specimen also conveyed the impression of osteogenic sarcoma. Although some penetration of the outer cortex was noted the marrow cavity of the femur was free of tumor thus confirming the periosteal origin of the neoplasm (Fig 196 *B*) Too little time has elapsed to tell whether or not a cure was effected in this instance.

Periosteal Osteogenic Sarcoma (Parosteal or *Juxtacortical Osteogenic Sarcoma).*—Considerable interest has been evinced recently in this category of unusual neoplasms, although somewhat obscure reference was made to them by Ewing in 1939 in his classification of bone tumors. They develop apparently through progressive active proliferation of bone forming periosteal connective tissue and appear on the surface of large limb bones rather than their interior The distal femur particularly is a site of predilection, though occasionally the tibia, the humerus, or some other long bone may be affected. They are said to be distinguished further from the conventional intramedullary osteogenic sarcomas by their more favorable course and substantially higher survival rate.[16] In the matter of appraisal, however it must be recognized that not all periosteal osteogenic sarcomas are comparable They appear to fall into two separate and distinct groups, comprising the ones that are clearly malignant from the start and those that seem to develop through subtle slow and gradual malignant change in certain lesions of juxtacortical osseous (and sometimes also cartilaginous) metaplasia. The former may be regarded as the periosteal counterpart of central or intramedullary osteogenic sarcoma. The latter may well be analogous to the comparatively rare sarcomas that develop through malignant change in lesions of myositis ossificans, as Jaffe and Selin have intimated.

The initially malignant periosteal osteogenic sarcomas are encountered so infrequently that relatively little is known as yet about their clinical behavior and appropriate treatment. *There are no informative precedents, for example to indicate*

whether one can resort with impunity to the expedient of block resection in an attempt to spare the affected limb or whether on the other hand ablation is mandatory I have had occasion to observe only 2 probable instances in point. One of them is the periosteal tumor previously mentioned whose periphery was composed predominantly of cartilage so that its basic osteogenic character was not clearly recognizable at the outset The other was a painful, progressively enlarging neoplasm that developed on the upper shaft of the tibia of a 5 year-old child over a period of observation of no more than 2 to 3 months In the roentgenogram one

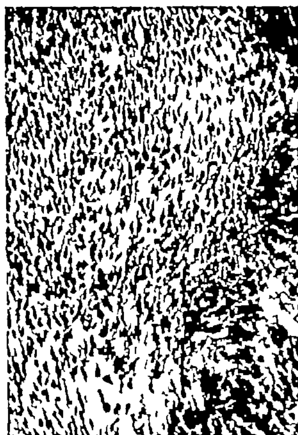


Fig 197—Photomicrograph of a selected field from a tumor on the upper shaft of the tibia of a child, showing active proliferation of periosteal fibroblastic connective tissue. The darker areas in the print reflect collagenization leading to osteoid and bone formation. (X175) (From Lichtenstein L., Tumors of Periosteal Origin Cancer 8, 1060 1955)

could discern a localized area of cortical thickening the outer convex surface of which appeared fuzzy ill defined and relatively radiolucent. The available biopsy sections showed condensed cortical bone interspersed with patches of newly formed osteoid and tracts of ominous-looking cellular fibroblastic connective tissue (Fig 197) The opinions expressed by the group of pathologists who studied the slides originally namely periosteal osteogenic sarcoma, ossifying periosteal fibrosarcoma, and periosteal osteoma, serve to highlight the problem in interpretation. Because of uncertainty as to the potential seriousness of this lesion the recommendation

of block excision was ventured, with the proviso that amputation without further temporizing should be considered in the event of aggressive local recurrence.

We come finally to the knotty problem of interpretation pertaining to the significance and potential seriousness of juxtacortical tumorlike masses of metaplastic bone and/or cartilage. These are not too uncommon and are situated most often on the lower femur posteriorly and occasionally on other limb bones (Fig. 198). In my own experience I have never observed a frank metastasizing sarcoma develop



A B

Fig. 198.—*A* and *B.* Roentgenograms illustrating periosteal (juxtacortical) ossification on the posterior aspect of the lower femur, its commonest site of localization. (From Lichtenstein, L.: Tumors of Periosteal Origin, Cancer 8: 1060, 1955.)

in these circumstances, even in instances followed for many years, and am therefore inclined to maintain a relatively conservative position in the matter of diagnosis and clinical management. Within the past several years, however, 2 documented papers have appeared expressing the view that, with few exceptions, such juxtacortical bony masses are sarcomatous from their inception and uniformly require early radical surgery. Because of the practical importance of their implications, these articles warrant critical detailed scrutiny.

The issue was first raised by Geschickter and Copeland in 1951 in a paper entitled *Parosteal Osteoma of Bone: a New Entity*. The main thesis of the paper as I understand it, is that parosteal bony masses of the type indicated are actually neoplastic, that the majority eventually become frankly malignant and that one should therefore incline toward radical surgical treatment (amputation of the affected limb) even in the absence of clear-cut evidence of sarcoma in biopsy specimens. A detailed analysis has been made of the case records outlined in the article cited and the breakdown is as follows. Of the 16 cases presented 8 seemed clearly to represent instances of ordinary metaplastic ossification (mainly on the lower femur —cases 2, 7, 8, 9, 10, 11, 12 and 14). Three additional cases (cases 4, 15 and 16) were apparently instances of genuine sclerosing osteogenic sarcoma from the beginning—in 2 of these (cases 15 and 16) the biopsy was obviously underdiagnosed. In another instance (case 6), the data are inconclusive for lack of any follow-up. That leaves but 4 cases in point in which pulmonary metastases are known to have developed after a significant interval. One of these (case 1) was originally reported by W. B. Coley in 1913 as a rare instance of malignant change in myositis ossificans and, on the basis of the evidence presented, I would agree. Another of these (case 13) had been previously irradiated at the site of sarcoma development, and the possibility of a post-irradiation sarcoma appearing after a long latent interval cannot be ruled out. In the 2 remaining cases (on which the validity of the authors' thesis rests) pulmonary metastases developed 5 and 9 years later, respectively (cases 3 and 5). In neither of these cases, however, was an autopsy performed, nor is any information given in regard to the local site, and since both patients were adults, the possibility of pulmonary metastasis from an independent cancer entirely unrelated to the skeletal lesion cannot be dismissed. On the basis of this analysis, I am inclined to question the validity of the conclusions drawn by the authors.

This thesis was subsequently expounded by Dwinnell, Dahlin, and Ghormley in 1954 in a paper entitled *Parosteal (Juxtacortical) Osteogenic Sarcoma*. The impression I gained from their presentation was that they regard virtually all bulky lesions of the type under discussion as low-grade osteogenic sarcomas, which should be treated empirically by prompt amputation, even though the histologic evidence of malignancy is so subtle as to be something like the Emperor's invisible clothes. Dahlin[a] has assured me, however, that this is not quite the impression he intended to convey and that he and his associates do recognize the existence of bulky lesions of parosteal ossification which are not malignant, although these are exceptional in their experience. At all events, analysis of the data presented indicates prima facie evidence of sarcoma (manifested in metastasis) in only 4 cases of the 15 cited and, without launching into specific details, suffice it to state that the remaining patients still under observation had apparently remained well for varying periods of time after treatment ranging up to 15 years. The obvious difficulty in interpretation here is that there can be no controls in individual clinical cases after amputation is performed. Nor can the reappearance of foci of ossification after conservative surgery be interpreted necessarily as indicating "tumor" recurrence—the same phenomenon may be observed after one operates prematurely on

an active lesion of myositis ossificans, for example. Incidentally the same criticism applies to a recent paper from the same source by Stevens, Pugh, and Dahlin, reporting on a somewhat larger group of patients (19 in all, 13 of whom were still alive after surgical treatment)

It is not my intention to deny the appreciable incidence of malignant change in lesions of periosteal (or juxtacortical) ossification. Apparently this is not so rare as it is in comparable lesions of myositis ossificans, perhaps because periosteal connective tissue has a greater growth potential than does the connective tissue of paraskeletal muscle. The pathologist must be on the alert for this serious complication, and it is incumbent upon him to sample thoroughly all the tissue submitted and particularly to scrutinize the fields of connective tissue closely In this connection, I believe that the rather subtle cytologic criteria for the diagnosis of early malignant change in such lesions need to be more clearly defined. Thus, in the *case in point illustrated in Fig 204 it was not until I had* examined material from the third surgical specimen (after a period of observation of over 6 years) that I observed sufficient change in the character of the connective tissue stroma to justify a recommendation of mid thigh amputation, by way of being on the safe side. Also in the case illustrated in Fig 203 as the legend indicates, fully 19 years elapsed after local excision before a "tumor" mass reappeared on the posterior shaft of the distal femur and an additional 11 years went by before this "recurrence" was resected. Further in regard to the lesions of parosteal or juxtacortical ossification illustrated in Fig 198 there was never any question of aggressiveness, even on clinical grounds. Altogether it would appear that the problem of reliable and foolproof pathologic appraisal of this group of lesions has yet to be resolved satisfactorily It may well be that the authors cited have been too radical, while I have been a bit too conservative, and the truth may lie somewhere in between. Pending further clarification, if limbs are not to be need*lessly sacrificed, it seems to me that the surgeon would be well advised in treating* pertinent cases to require convincing pathologic proof of malignancy rendered by an experienced observer before resorting to radical surgery The current practice at some large clinics of rushing into amputation even without biopsy is, in my opinion, to be deprecated.

Summary

This chapter presents a comprehensive discussion, in so far as available data will permit, of tumors developing apparently within periosteal connective tissue. These comparatively uncommon neoplasms constitute a group unto themselves and their biologic and clinical behavior can only be ascertained empirically Specific reference is made to periosteal fibroma, neurofibroma, lipoma, and chondroma as the major benign tumors in point and to fibrosarcoma, chondrosarcoma, and osteogenic sarcoma as the malignant ones. Also considered is the significance of cartilaginous and/or osseous metaplasia of periosteal connective tissue leading to the formation of juxtacortical (parosteal) tumorlike masses and the incidence of malignant change in such lesions. The position taken is one of opposition to indiscriminate radical surgery as has been advocated recently

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APPENDIX I

Some Non-Neoplastic Lesions of Bone Which May be Mistaken for Tumors

The emphasis upon early diagnosis of malignant tumors as a means of reducing mortality has also been carried over into the field of bone tumors. Unfortunately this principle has limited application here inasmuch as certain malignant tumors are already far advanced when first recognized clinically while others tend ultimately by their very nature to involve many bones, in spite of prompt vigorous therapy directed against the presenting lesion. It is true that chondrosarcoma developing through subtle malignant change in a benign enchondroma or an osteocartilaginous exostosis is not always recognized as early as it might be and that such delay may sometimes mean the difference between cure and ultimate fatality This urgency may apply also to instances of central fibrosarcoma and of primary reticulum-cell sarcoma of bone which can often be cured if they are appropriately treated before metastasis has developed. On the other hand an osteogenic sarcoma frequently spreads to the lungs so early that a tumor of which the patient has been aware only a few weeks carries as serious a prognosis as one which is known to have been present for a number of months. Also, the chances for cure when dealing with Ewing's sarcoma or with myeloma and other tumors of hematopoietic origin (exclusive of primary reticulum-cell sarcoma) are not very bright in any event, since these neoplasms tend strongly to dissemination throughout the skeleton, even when this is not clinically or roentgenographically discernible.

It is my impression that in the matter of recognizing and treating skeletal tumors in general more mischief is done currently through overdiagnosis than though failure to recognize malignant neoplasms promptly Much of this can be obviated by seeking expert opinion, whereby it is often possible to forestall or avert unnecessary radical surgery for lesions which are less serious than they were at first considered to be by the clinician, radiologist, or pathologist as the case may be. As examples of benign tumors which are sometimes overdiagnosed and

hence treated more radically than is necessary one may cite instances of benign chondroblastoma and chondromyxoid fibroma mistaken for chondrosarcoma of bulky though not actively growing osteocartilaginous exostoses mistaken for chondrosarcoma, as well as osteogenic sarcoma of benign osteoblastoma mistaken for osteogenic sarcoma and of non-osteogenic fibroma mistaken for giant-cell tumor or even for low-grade fibrosarcoma



Fig 199—Roentgenogram of a bone cyst in its common location the upper metaphysis of the humerus, showing a pathologic fracture. Lesions such as this are still mistaken on occasion for giant-cell tumor though without much justification.

It is important to recognize also that certain non neoplastic lesions of bone may sometimes be mistaken for tumors. It is common knowledge for example, that on occasion infections, especially acute or subacute osteomyelitis of a long bone which has provoked rapid periosteal new bone apposition, may simulate Ewing's tumor clinically and roentgenographically In fact, even after exploration the surgeon may not be *quite certain whether he is dealing* with one condition or the other

inasmuch as it may be difficult under such circumstances to distinguish clearly pus from softened, necrotic tumor tissue. Similarly a solitary lesion of eosinophilic granuloma of bone (in a rib or a long bone, for example) may also simulate Ewing's tumor clinically since it tends rather rapidly to break through the cortex of the affected bone and extend into the adjacent muscle tissue. By the same token, cases of eosinophilic granuloma of bone presenting multiple defects in the calvarium, pelvis, and long bones may at first simulate instances of metastatic tumor especially neuroblastoma. Here again, clarification of the diagnosis must often await pathologic examination of a biopsy specimen.



Fig. 200.—Remarkable, expanded tumorlike lesion of Gaucher's disease in an old woman, who had been aware of a mass in her left shoulder region for more than 30 years.

By way of citing other instances in point, one may mention that occasionally the common bone cyst[3] is mistaken for giant-cell tumor with untoward consequences. I recall a pertinent case in which a bone cyst in the upper metaphysis of the humerus of a child was heavily irradiated on the premise that it represented a giant-cell tumor (despite its location and the youthfulness of the patient) In this instance a fibrosarcoma developed several years later at the site of irradiation, necessitating *disarticulation of the extremity* It is also *relevant* here to point out that the peculiar lesion which we designated as aneurysmal bone cyst has been mistaken in the past for giant-cell tumor (atypical subperiosteal giant-cell tumor so-called) and occasionally for osteogenic sarcoma.

Further it is not too unusual for localized rarefied defects resulting from hyperparathyroidism to be confused with genuine giant-cell tumors so that attention is diverted from a search for the offending parathyroid adenoma and valuable time lost thereby It is interesting to note also that the rather large, circumscribed skeletal defects reflecting the early resorptive changes in Paget's disease may likewise prove confusing Their appearance and significance in the calvarium are well recognized



Fig 201 – A Roentgenogram of a lesion of gummatous syphilis in the tibia, which might be mistaken by some for a bone sarcoma There is also apparent cortical thickening of the contiguous fibula B Pathologic fracture with exuberant callus in an ulna which healed under antisyphilitic therapy The lesion was at first considered to be an osteogenic sarcoma by some observers The patient is known to have been well 8 years later

(so-called osteoporosis circumscripta cranii) but it is not generally appreciated that comparable defects may develop in other bones, e.g the innominate bone or a tibia, as a forerunner of typical Paget transformation (Fig 213)

Continuing in the same vein a solitary focus of fibrous dysplasia of bone may readily be mistaken for a benign neoplasm of one kind or another if one is not altogether familiar with its roentgenographic and pathologic characteristics. Thus,

it is not uncommon to find pertinent lesions in jaw bones particularly labeled as fibrous osteoma or ossifying fibroma, or lesions in large limb bones such as the femur or tibia interpreted as non-osteogenic fibroma. I am also aware of several instances in which a relatively large lesion of fibrous dysplasia in a limb bone, occupying a substantial part of the shaft, was overdiagnosed as osteogenic sarcoma. When confronted with a solitary focus of fibrous dysplasia in a rib, a common location for it, radiologists seem prone to misinterpret such a lesion as a central cartilage tumor despite its rather distinctive appearance (Fig. 205 *A*).

In dealing with lesions held to represent osteogenic sarcoma, one must be particularly careful before resorting to ablation or radical resection to make certain that the condition does not represent some other less serious lesion exhibiting active new bone formation for whatever reason.[1, 16] That this problem in differentiation may at times constitute a formidable pitfall is evidenced by the fact that the 5 year cures of osteogenic sarcoma so-called are undoubtedly padded by cases of periosteal ossification, myositis ossificans (in an active stage), ossifying hematoma, and exuberant fracture callus, among other conditions (see p. 210). I have personal knowledge of an appreciable number of such cases in which review of the pertinent roentgenograms and pathologic specimens indicated clearly that the lesions in question had been overdiagnosed and that a surgical procedure far less drastic than amputation would have effected a clinical cure. It seems to be true unfortunately that pathologists not well versed in the subtleties of the diagnosis of skeletal lesions are sometimes stampeded into a diagnosis of osteogenic sarcoma by the observation of active osseous and cartilaginous metaplasia of connective tissue, even though the latter is situated outside of the bone and the background of the lesion as a whole is not that of an osteogenic sarcoma. It is important in this connection to stress once again that pertinent information in regard to the clinical history, the roentgen picture, and the surgeon's findings is essential in arriving at an intelligent opinion, self-evident though this may seem.

In such instances, one must be guided further by the principle that one must appraise a lesion in the light of its probable ultimate behavior rather than by its seemingly ominous cytologic appearance at the height of its activity. Stated more explicitly, localized foci of active osseous, and sometimes also cartilaginous, metaplasia of the connective tissue of muscle (so-called myositis ossificans), of the periosteum, and very occasionally of the intramedullary connective tissue as well, tend with few exceptions to be self limited rather than progressive. That is to say, they burn themselves out eventually in the sense that in their end stage they come to be matured and reconstructed bony masses incapable of further significant growth. This appears to be true whether the lesion develops as a result of an injury (with or without associated hemorrhage) or whether it develops spontaneously due to causes unknown. Experienced orthopedic surgeons are well aware of this trend and of the desirability of waiting until the process of metaplastic ossification has fully subsided, rather than operating prematurely at the risk of provoking renewed activity. One must take cognizance of the fact, however, that there are a few cases in the literature indicating that on rare occasions sarcoma may develop at a site of myositis ossificans[14] or of an ossifying hematoma[3] and lead to fatal pulmonary

metastases. I have never observed such instances in my own experience and for that matter (quite aside from any consideration of myositis ossificans as a predisposing factor) I have encountered relatively few neoplasms that could be plausibly interpreted as extraskeletal osteogenic sarcoma, although neoplastic bone and cartilage may occasionally make their appearance as integral neoplastic components of malignant mesenchymal tumors of soft parts.

As noted exuberant callus developing at a site of pathologic fracture due to whatever cause may sometimes be misinterpreted as an indication of a sclerosing osteogenic sarcoma I have had occasion to review a case in which a pertinent lesion in an ulna, thought at first to represent a sarcoma, proved subsequently to be



Fig. 202.—Low-power photomicrograph of a somewhat unusual instance of periosteal cartilaginous and osseous metaplasia leading to the formation of an exostotic tumor clinically and roentgenographically The new bone formed by ossification of cartilage is layered over the original cortex (of a femur)

a gumma. Fortunately the pathologist who interpreted the biopsy sections, though leaning in favor of osteogenic sarcoma, took so long to reach a definite decision that sufficient time elapsed for the lesion to heal under antiluetic therapy (Fig 201 *B*) Apropos of this case and others like it, experienced radiologists need scarcely be reminded that in dealing with equivocal skeletal lesions, as with equivocal lesions elsewhere, it is important to have the benefit of essential clinical data. In regard to the problem of pathologic interpretation, it may be helpful to emphasize again, as previously noted that before a lesion can be interpreted as an osteogenic sarcoma one must be certain that it is actually a sarcoma in the first place. In other words, however extensive or *otherwise impressive the tendency to new bone formation may*

be, an essential prerequisite for the diagnosis of osteogenic sarcoma is the presence of a connective tissue stroma which is frankly sarcomatous. This is not intended to imply that the distinction is invariably a simple one to make (as was true of the case cited previously) and there are undoubtedly instances which call for nice judgment and mature experience.

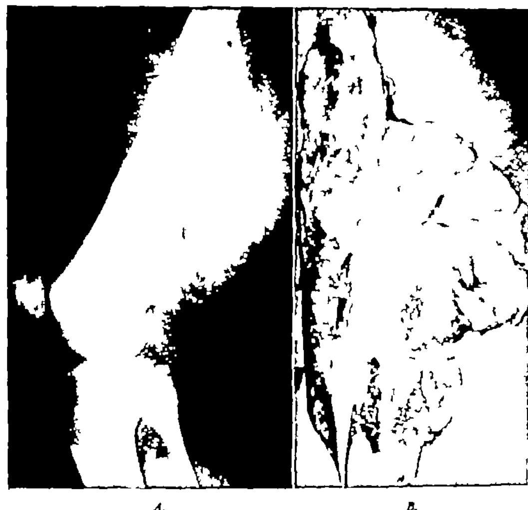


Fig. 203.—*A* and *B*. Roentgenogram and photograph of resected specimen from a remarkable case of metaplastic cartilage and bone formation within the connective tissue of the periosteum and/or the adjacent muscle tissue simulating chondrosarcoma. The patient had had a mass excised from the shaft of the femur 30 years previously; this mass reappeared 19 years later and slowly progressed in size for about 11 years up to the time of resection. (Courtesy of Dr. Lauren V. Ackerman, St. Louis.)

The remainder of this discussion will be devoted to further consideration of a limited number of specific lesions of bone, which deserve special comment for one reason or another: namely, fibrous dysplasia of bone, the skeletal manifestations of histiocytosis X (eosinophilic granuloma, Schüller-Christian disease, and Letterer-Siwe disease), aneurysmal bone cyst, the skeletal changes in hyperparathyroidism, and monostotic Paget's disease.



A



B

Fig. 204–4. Roentgenogram of an unusual instance of metaplastic ossification simulating osteogenic sarcoma. The process involved not only the connective tissue of muscle and the periosteum but also the intramedullary connective tissue. Local excision in an attempt to eradicate the lesion was performed on three separate occasions over a period of about 6 years. *B*, Photomicrograph of a representative field of the intramedullary portion of the lesion illustrated in *A* showing fibrosis of the marrow and new bone formation within it. The appearance of this fibrous stroma is hardly that of an osteogenic sarcoma. (×120.) Amputation was performed after the third operation because of the surgeon's concern that the lesion represented an insidiously developing parosteal or juxtacortical osteogenic sarcoma. The patient has shown no evidence of metastasis to date.



Fig. 203.—*A* Roentgenogram of a fusiform expanded, tumorlike lesion in a rib which was resected and proved to be a focus of fibrous dysplasia. It was discovered in a routine chest film and was apparently the only lesion the patient presented. *B* Photomicrograph of a representative field from a comparable lesion of fibrous dysplasia. Note the delicate spindly connective tissue stroma, in which curlicues of metaplastic bone have been deposited, mainly along the course of blood vessels.

Fibrous Dysplasia of Bone

My interest in fibrous dysplasia of bone dates back to 1938 when I described the distinctive skeletal pathologic changes and coined the name "polyostotic fibrous dysplasia" to designate them appropriately Subsequently the qualifying adjective "polyostotic" was dropped when it became evident that in many instances only a single bone is involved The finding of associated skin pigmentation and of certain endocrine abnormalities, especially precocious sexual development in female patients, had previously been noted by Goldhamer and by Borak and Doll among others, and emphasized particularly by McCune and Bruch and by Albright and his

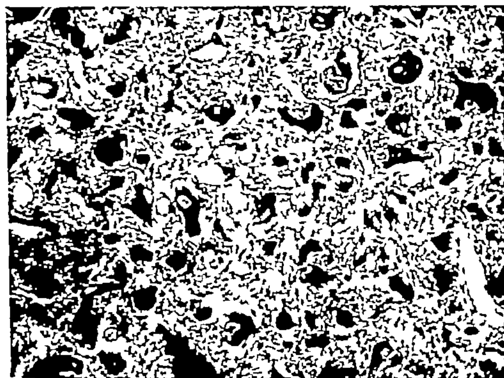


Fig. 206—Photomicrograph of a lesion of fibrous dysplasia which presented as a rather small, circumscribed, lytic defect in a calvarium. *This is a distinctive pattern frequently observed* in lesions of fibrous dysplasia which develop within bones preformed in membrane (calvarium and jawbones) (×100.)

associates. The latter group especially subsequently publicized these more dramatic cases in children presenting various extraskeletal abnormalities, as well as widespread severe skeletal alterations, and accomplished this so effectively that the changes described came to be designated as Albright's syndrome, although Albright himself has since recommended that the name fibrous dysplasia be generally adopted to apply to all pertinent cases of the disorder irrespective of their severity

In 1942 Jaffe and I[13] reviewed the entire subject on the basis of greater experience with it and expressed the view that the disease as a whole apparently represents a peculiar developmental anomaly in which the basic skeletal changes



Fig 207 — *A* and *B* Photomicrographs showing additional patterns seen in fibrous dysplasia. The lesion in *B* also shows an island of hyaline cartilage heavily calcified around its periphery

common to all cases may be supplemented particularly in the more severe instances by various extraskeletal aberrations specifically blotchy pigmentation of the skin, premature sexual development premature skeletal growth and maturation and hyperthyroidism, as well as cardiovascular and other developmental defects. The skeletal lesions apparently result from perverted activity of the bone forming mesenchyme. The affected bone areas may be expanded bowed and otherwise deformed and are filled with a distinctive whitish rubbery and somewhat gritty fibrous tissue which in occasional instances may also contain more or less prominent islands of hyaline cartilage While occasional patients may exhibit the florid expression of the disorder in early childhood, many more show limited skeletal involvement, often predominantly unilateral or monomelic and the great majority (frequently adults) present only a single bone lesion, or a few at most and by way of extraskeletal changes nothing more than perhaps an occasional patch of hyperpigmented skin

By way of differential diagnosis, it is worth noting that adult patients with fibrous dysplasia involving several or many bones are sometimes thought to have hyperparathyroidism and may even be subjected to a search for a parathyroid adenoma. I have knowledge of an appreciable number of such cases, and the literature contains reference to many more. Solitary foci of fibrous dysplasia, on the other hand are not infrequently mistaken for tumors and, as such, treated more vigorously than is necessary (e g by block excision) Actually their surgical removal is usually elective rather than mandatory If such a lesion, however is still expanding (in a jawbone for example) is painful or cosmetically deforming or is prone to pathologic fracture, clinical cure can usually be accomplished by thorough curettement and packing with bone chips. On occasion, if the defect thus created is sufficiently large or so situated as to necessitate reinforcement of the affected area, one may resort to the use of an additional inlay strut.

It is also pertinent here to consider briefly the question of malignant change in skeletal lesions of fibrous dysplasia. To my knowledge, this has never been observed in a patient presenting only a single focus. With reference to the polyostotic expression of the disorder a number of cases have been recorded by Sutro, Coley and Stewart, and Perkinson and Higinbotham of sarcoma developing in bones containing well-established lesions of fibrous dysplasia. In none of these instances, however was convincing pathologic proof elicited to establish direct causal relationship rather than coincidence.

Histiocytosis X (Eosinophilic Granuloma of Bone, Schüller-Christian Disease and Letterer-Siwe Disease)

In a review article[9] in 1953 under the above heading I surveyed the accumulated evidence indicating that eosinophilic granuloma, Schüller-Christian disease and Letterer-Siwe disease are all interrelated expressions of the same malady for which the provisional designation of histiocytosis X was proposed for convenient reference. There are many features of the disease complex to suggest that it represents a reaction to some peculiar infection (possibly viral) although we have no clue as yet to the nature of the etiologic agent According to this concept the lesion of eosinophilic granuloma seems to represent the pathologic expression of early



Fig 206.—*A* and *B* Roentgenograms from a case of eosinophilic granuloma in a young child showing lytic, tumorlike defects in the calvarium and also in the wing of an iliac bone *C* Photomicrograph of a field from a lesion of eosinophilic granuloma showing (eosinophilic) leukocytes intermingled with histiocytes. (×400.)

rather rapidly developing reaction to the etiologic agent and, as such, it may appear not only within bone where its presence was first recognized but also in other sites as well, notably in lymph nodes, the skin the oral cavity (gingiva palate etc.) and the anogenital region, as well as in the lungs and possibly other viscera (if the whole picture were to be revealed) It may be encountered not only as a skeletal lesion per se in which case the prognosis is favorable but also as a destructive

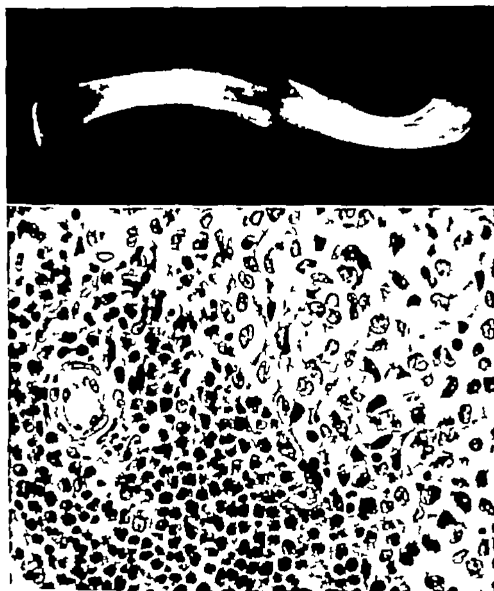


Fig. 209—*A* Roentgenogram of a surgically removed clavicle showing pathologic fracture through a destructive tumorlike lesion which proved to be an eosinophilic granuloma. Had the surgeon been aware of this possibility conservative biopsy followed by roentgen therapy would have sufficed for cure *B* Photomicrograph of a lesion of eosinophilic granuloma. The leukocytes massed on the left are all eosinophiles; the larger cells to the right are of histiocytic nature. (×450)

skeletal focus developing in the clinical course of either the Letterer-Siwe or the Schüller-Christian syndrome. The latter apparently represents the acute (or subacute) and chronic forms, respectively of the same systemic malady Collaterally the old idea stemming from Rowland and Thannhauser that so-called Schüller Christian disease represents a disorder of lipid metabolism is no longer tenable.

Classification of Histiocytosis X

Histiocytosis X, localized to bone (eosinophilic granuloma solitary or multiple)

Histiocytosis X, disseminated, acute or subacute (Letterer-Siwe syndrome)
- With destructive skeletal lesions (eosinophilic granuloma)
- With transition to chronic phase (Schüller Christian syndrome)

Histiocytosis, disseminated chronic (Schüller-Christian syndrome)
- With destructive skeletal lesions (eosinophilic granuloma)
- With early extraskeletal lesions (indicate sites) resembling eosinophilic granuloma
- With acute or subacute exacerbation (Letterer Siwe syndrome)
- With involvement predominantly of bones, lungs, pituitary and/or brain, skin, mucous membranes, (oral anal genital) liver or lymph nodes, etc. (in varying combinations, as the case may be)

In regard to therapy and prognosis, we now know that the acute disseminated form of the disease (Letterer-Siwe) is not invariably fatal and that some infants and young children can be carried along for years into a more chronic phase (*Schüller-Christian*) *Similarly even in relatively serious, progressive cases* of the chronic disseminated expression of the disease (Schüller-Christian) in adults, as well as children, presenting diabetes insipidus and/or extensive pulmonary infiltration as their major problem, it is often possible by alert and well-conceived clinical management to ward off a fatal outcome for some time and occasionally to induce a remission. Such management is concerned mainly with abatement of skeletal and extraskeletal foci through the use of adequate roentgen therapy general supportive measures, prevention and control of potentially serious secondary infections by the judicious use of antibiotics, amelioration of diabetes insipidus by the use of Pitressin or irradiation and the use of steroid (cortisone) therapy

Aneurysmal Bone Cyst

The distinctive lesion we called aneurysmal bone cyst[6, 7, 8, 12] represents a not uncommon pathologic entity which is gradually gaining general recognition, although, as noted, individual instances of it are still mistaken by some for an unusual type of giant-cell tumor and even for osteogenic sarcoma. In a recent survey[8] I commented on observations gleaned from as many as 50 cases (encountered since 1948) The lesion develops in vertebrae and flat bones, as well as long bones. The affected site, whatever its location may be, is completely transformed and ultimately comes to resemble a peculiarly expanded, brownish, blood filled sponge, which, if untreated, may attain impressive size The communicating pools of venous blood within this reservoir are bordered by connective tissue septa showing giant-cell reaction, especially within fields of blood extravasation, as well as more or less conspicuous reparative new-bone formation, by way of attempted reconstruction. In regard to pathogenesis, I favor the view that the condition apparently results from some



Fig 210 — *A* Roentgenogram of an aneurysmal bone cyst originating in and protruding from the upper end of an ulna. *B* Photograph of the same lesion after it had progressed for another year (Amputation was performed because useful reconstruction was no longer deemed feasible.) The lesion was spongelike in its architecture and composed of innumerable dilated blood filled spaces lined by fibro-osseous septa. *C* Photomicrograph of a representative field of an aneurysmal bone cyst showing its essential pattern. Other fields may show more active osseous reconstruction or giant-cell reaction to hemorrhage.

local circulatory disturbance, leading to markedly increased venous pressure and the development of a dilated and engorged vascular bed within the affected bone area.

Aneurysmal bone cyst is not serious, if recognized and treated promptly, although it can have serious consequences if neglected (e.g., loss of a limb or spinal cord damage) It responds satisfactorily to thorough curettement and can be controlled also by roentgen therapy in moderate dosage. The latter is the treatment of choice in dealing with lesions in vertebral bodies or their neural arches, where an attempt at surgical extirpation might be hazardous.

Skeletal Changes in Hyperparathyroidism

In the modern era of early parathyroid surgery for suspected tumor one seldom has the opportunity any longer to observe the devastating skeletal changes of "osteitis fibrosa cystica generalisata" of Recklinghausen. *If one wishes to observe the curiously bent, broadened, extremely porotic and fractured bones reflecting the natural end stage of hyperparathyroidism, one must have recourse to museum specimens dating back 25 years or more. Today one is more likely to observe rather subtle roentgen evidences of skeletal resorption, such as cortical rarefaction and subperiosteal scalloping requiring close scrutiny for their detection, and sometimes even these are lacking In other instances it is true the skeletal effects of hyper parathyroidism may be more pronounced and find expression in distinct cortical thinning of long bones, the presence of cystlike rarefactions (at sites of brown tumor so-called) or perhaps pathologic fracture through a demineralized bone, going on to non-union. In such cases, if one is aware of the possibility of hyperparathyroidism confirmatory evidence of the diagnosis leading to surgical exploration will be readily furnished by such findings as granular mottling of the calvarium, nephrocalcinosis and attendant renal damage, and significant serum chemical alterations, particularly persistent hypercalcemia and increased serum alkaline phosphatase activity

If the observer is not alerted to the possibility of hyperparathyroidism by the history and the skeletal roentgen changes, he may be led to suspect carcinomatosis or multiple myeloma, or perhaps senile or idiopathic osteoporosis. Also it is not too unusual for localized rarefied defects resulting from hyperparathyroidism to be confused with giant-cell tumor as previously noted.

The treatment of primary hyperparathyroidism consists, of course, of surgical removal of the hyperfunctioning parathyroid tissue. In the great majority of instances, this will prove to be an adenoma of a single gland, although occasionally there may be two adenomas and, sometimes, hyperplasia of all four glands. The technical aspects of parathyroidectomy and the problems relating to post-operative care are beyond the scope of this discussion. It may be in order however, to emphasize as is now well known, that the surgeon must be prepared, if necessary to search for an aberrant adenoma in the vicinity of the esophagus or in the superior mediastinum and to safeguard by appropriate means against renal suppression, as well as temporary hypoparathyroidism manifested in tetany





Fig 211 —*A* Roentgenogram of a tibia and fibula from a proved case of hyperparathyroidism with far advanced skeletal changes. (The patient had also sustained a pathologic fracture of a femur which failed to unite) *B* A representative field of a biopsy taken from the tibia showing extensive resorption and fibrous replacement of the bone as well as conspicuous giant-cell reaction at a site of hemorrhage (so called "brown tumor") (×100.)

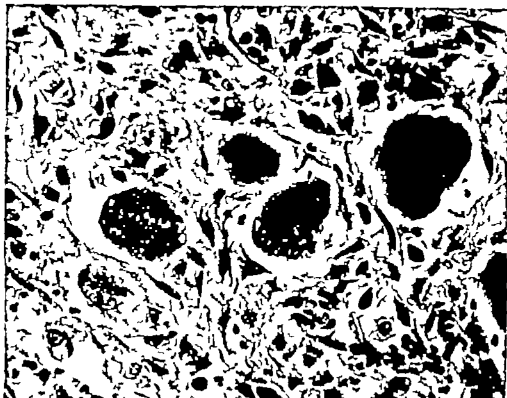


Fig 212.—A field from a brown tumor so called, in another case of hyperparathyroidism intended to show that the large multinuclear cells are lodged within blood channels. This picture is quite different from that of genuine giant cell tumor (see Figs. 65 and 66, taken at the same magnification) (×420)

Paget's Disease (Monostotic)

This section will deal briefly with the recognition of relatively early monostotic lesions of Paget's disease, which still prove puzzling to many surgeons and radiologists. Just as foci of intense resorption and fibrous replacement of bone in hyperparathyroidism may be manifested roentgenographically in the appearance of localized defects sometimes mistaken for tumors (especially giant-cell tumor) so, too the sizeable circumscribed skeletal defects reflecting the early resorptive changes in Paget's disease may likewise prove confusing at times. Their appearance and significance in the calvarium are now well recognized (so-called osteoporosis circumscripta cranii) It seems not to be generally appreciated, however that comparable defects may develop in other bones, e.g., an innominate bone, a tibia or a humerus, as a forerunner of typical Paget transformation. When the tibia is involved, it is frequently the upper half of the shaft that is affected although occasionally the lower end may display comparable changes (Fig 213 *A* and *B*) The rarefied defect often terminates sharply and is likely to be associated with some expansion of the shaft and thinning of its cortex, although there is not as yet any discernible coarse-trabecular architecture Altogether if one is alert to the possibility the



A *B* *C*

Fig. 213 — *A* and *B* Roentgenograms of two instances of early monostotic Paget's disease involving the lower tibia. The lesion in each instance is still in a phase of active resorption and does not as yet show typical Paget transformation. *C* Photomicrograph of a field from the biopsy of the lesion of Paget's disease illustrated in *B* (×75)

roentgenographic picture of such lesions is sufficiently distinctive to suggest early monostotic Paget's disease (rather than a neoplasm or fibrous dysplasia) and even at this stage of its evolution, the microscopic changes observed in a biopsy specimen can be readily identified as those of Paget's disease (Fig 213 *C*). Treatment in such cases is concerned mainly with the relief of pain and discomfort and with reassuring the patient that the condition, if it remains localized, is not likely to have serious consequences.

The problem of sarcoma complicating Paget's disease is an important one, but this has already been discussed in the chapter on osteogenic sarcoma.

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APPENDIX II

Tumors of Synovial Joints, Bursae, and Tendon Sheaths

Although growths of joints, bursae and tendon sheaths are of course, not bone tumors, they do quite often develop in intimate association with contiguous bones and at times may erode and even extend into them. It was felt, therefore, that their comprehensive discussion in a chapter in the Appendix might enhance the usefulness of the book. This chapter includes the material presented in my survey in *Cancer*[34] in 1955 with some additions and minor changes to bring the subject up to date.

In view of their close pathologic relationship it appears logical, as well as expedient, to consider the linings of synovial joints, bursae, and tendon sheaths as a single unit for the purpose of discussing tumors and tumorlike lesions. The deeper fibrous component of articular capsules and bursal walls, as well as the relatively inert tendons themselves scarcely enter seriously into the problem of neoplastic proliferation, except in so far as one may note the rare occurrence of ordinary fibroblastic tumors.

In the pertinent literature[19] one finds a number of lesions broadly classified as tumors that are not genuine neoplasms or whose pathologic interpretation is debatable. Thus, the common ganglion, developing as it does through myxoid degeneration and cystic softening of the connective tissue of a joint capsule or tendon sheath, constitutes a tumor only in the limited clinical sense of a swelling (Fig 214) Further the condition of synovial bursal, or tenosynovial osteochondromatosis may be convincingly interpreted as a self limited metaplastic process rather than a genuine expression of neoplasia, as will be indicated presently Continuing the tumorlike lesions that have been called giant-cell tumor xanthomatous giant cell tumor giant-cell myeloma, benign synovioma, and giant-cell synovioma (among other names) have long been a subject of controversial interpretation. There are some, I among them, who feel that they may well represent peculiar hyperplastic

granulomas of as yet undetermined etiology rather than bona fide neoplasms. This concept is implied in the designation of pigmented villonodular synovitis, bursitis, and tenosynovitis,[28] as the case may be.

If one sets apart the conditions mentioned, there are actually relatively few undisputed tumors that are observed with any appreciable frequency. The benign tumors that are encountered occasionally on the lining surfaces of articular capsules and tendon sheaths are mainly of the nature of lipomas and hemangiomas, derived from the supporting fatty connective tissue and its blood vessels. Fibroma and chondroma also are listed in some classifications,[7, 28] but their occurrence, at least in the sense of genuine tumors of fibroblasts and chondrocytes respectively, seems



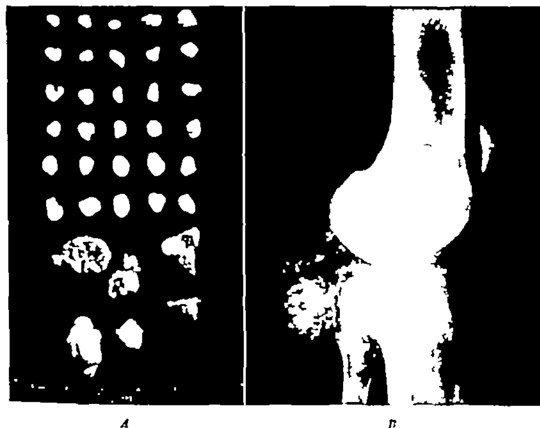
A B

Fig. 214.—*A*, Ganglion formation through myxoid change and cystic softening of the connective tissue of a joint capsule. (×8.) *B*, Comparable multilocular cyst formation within the parameniscal connective tissue of a knee joint. (×9.) (From Lichtenstein, L.: Tumors of Synovial Joints, Bursae and Tendon Sheaths, Cancer 8: 816, 1955.)

questionable. At all events if they do occur they must be so rare as to constitute pathologic curiosities. As for primary malignant neoplasms, the only one of practical importance is synovial sarcoma. This ominous neoplasm is being recognized with increasing frequency by pathologists, now that its specific cytologic features have been well defined, although the problem of effective treatment is still a formidable one. While the finding of such tumors as malignant hemangioendothelioma, liposarcoma, fibrosarcoma, and chondrosarcoma, among others, is theoretically possible, actual recorded experience with them in the sites under consideration appears to be virtually nonexistent.

TUMORLIKE LESIONS OF DEBATABLE PATHOLOGIC NATURE

It seems appropriate here to consider further the nature of two specific lesions of uncertain pathogenesis which may simulate tumors in their gross, if not in their microscopic appearance These have been already mentioned and are chondromatosis (or osteochondromatosis) of joints, bursae and tendon sheaths and pigmented villonodular synovitis, bursitis and tenosynovitis (so-called giant-cell tumor or giant-cell synovioma) This consideration is of practical importance as well as academic interest, having a bearing on appropriate treatment.



A B

Fig. 215 —*A* Photograph of numerous chondral and osteochondral joint bodies removed from an elbow in a case of osteochondromatosis. *B* Roentgenogram of a lesion of osteochondromatosis of a popliteal bursa. Pictures such as this are sometimes misinterpreted as indicating the presence of chondrosarcoma. (From Lichtenstein L., Tumors of Synovial Joints, Bursae and Tendon Sheaths, *Cancer 8: 816 19*)

Osteochondromatosis

This condition is featured by the formation of numerous chondral and osseous bodies within the lining and sublining connective tissue of the affected structure. It is encountered far more often in joint capsules than in bursae or tendon sheaths, and the knee joint is its commonest site although occasionally a hip an elbow or some other joint may be affected (Fig 215 *A* and *B*) When a knee joint is

involved for example, one may observe (on surgical exploration in the course of synovectomy) that the synovial lining of the joint proper and perhaps of the suprapatellar pouch and posterior compartment as well, is studded by innumerable, small firm, flat or slightly raised, gray yellow nodules. These have a tendency to become extruded so that the joint may contain numerous, sometimes hundreds, of free chondral bodies. Whether or not these may be visualized roentgenographically depends upon whether they show sufficient calcification or osseous transformation to be radiopaque.

On microscopic examination of the lining of an affected joint, one observes numerous foci of cartilagenous and/or osseous metaplasia in varying stages of development. The cartilage foci as noted, may become calcified or converted to bone.



Fig. 216—Synovial chondromatosis (knee joint) Some of the chondral bodies are calcified, but there was no osseous metaplasia in any of the sections examined (×35.)

At such sites there is initially focal nodular condensation of the connective-tissue cells, but the synovial lining elsewhere shows no characteristic alteration (Fig 216) Once the chondral or osseous bodies are formed, their growth potential appears to be distinctly limited. While the number of such bodies and conglomerate aggregates of them may be impressive at times, there appears to be no compelling reason to regard the process as neoplastic and I have no knowledge of any instance in which malignant change actually ensued. Freund and others have also expressed the view that the condition described represents a self limited metaplastic process analogous to myositis ossificans. In fact, spontaneous arrest and regression have been noted clinically by a number of observers,[17, 38] which is scarcely the behavior one would expect of a neoplasm.

Pigmented Villonodular Synovitis, Bursitis and Tenosynovitis

This is the descriptive name I and my colleagues[23] devised in 1941 for a distinctive yellow brown villous and/or nodular lesion encountered in joints and bursae as well as in tendon sheaths. As indicated in the original paper, this lesion may take a number of forms, depending upon its site and whether it is localized or more diffuse, but it has the same essential character pathologically in all these circumstances Thus, it was pointed out that the diffuse villous or villonodular expression in joints *(commonly a knee joint) has its precise counterpart in bursae and its equivalent* expression in tendon sheaths, although the latter is seen comparatively infrequently The usual form of tendon-sheath involvement is, of course, the familiar localized nodule (generally solitary but occasionally mutiple) previously designated as giant cell tumor or myeloplaxoma by some and as xanthoma or xanthogranuloma by others (Fig 217 A) It was further demonstrated that this tendon sheath nodule is cytologically indistinguishable from the sessile or pedicled nodules observed in lesions of pigmented villonodular synovitis or bursitis. In an early stage of its evolution, it may likewise present a villonodular pattern, thus definitely linking it pathogenetically to the synovial and bursal equivalents of the condition.

For the sake of brevity the complex cytologic details of the lesion in all these circumstances will not be reiterated here. Suffice it to state that, whatever its localization, the lesion in general is characterized in its early stages by appreciable vascularity and conspicuous hemosiderin deposition, as well as villous hypertrophy of the lining of the affected structure and agglutination of villi to form synovial-lined clefts. These eventually become incorporated in webbed, matted, or more solid areas (Fig 217 *B*) Concomitantly one observes active proliferation of cells (occasionally in syncytial aggregates constituting giant cells) that appear to have a dual origin, being derived in part from synovial lining cells that have migrated downward and, in part, from the adventitial reticular cells of blood vessels At all events, these prominent stromal cells, which may dominate the picture in an active lesion soon manifest their tendency to function as macrophages through phagocytosis of hemosiderin as well as lipid (usually cholesterol esters) Eventually many lesions *tend spontaneously to involute in part or throughout, as a result* of extensive fibrosis and collagenization It seems altogether probable, incidentally that roentgen ray therapy accelerates this change. This evolutionary cycle may go on to substantial completion, as it commonly does in tendon-sheath nodules of long standing, or may renew itself as it does in the more exuberant lesions in the knee joint or in the popliteal space

It is of practical importance to emphasize that at the height of proliferation of the histiocytic stromal cells, and especially before their phagocytic tendency becomes quite obvious, a casual observer unfamiliar with the lesion may gain the impression that it is a sarcoma In fact not a few pertinent cases in the literature have been reported as such,[24] and undoubtedly many instances in the past have been treated by unnecessarily radical surgery I have personal knowledge of several, seen in consultation, in which amputation of a lower limb had been seriously contemplated. In my own experience to date, I have not observed a single instance of pigmented villonodular synovitis, bursitis, or tenosynovitis in which malignant

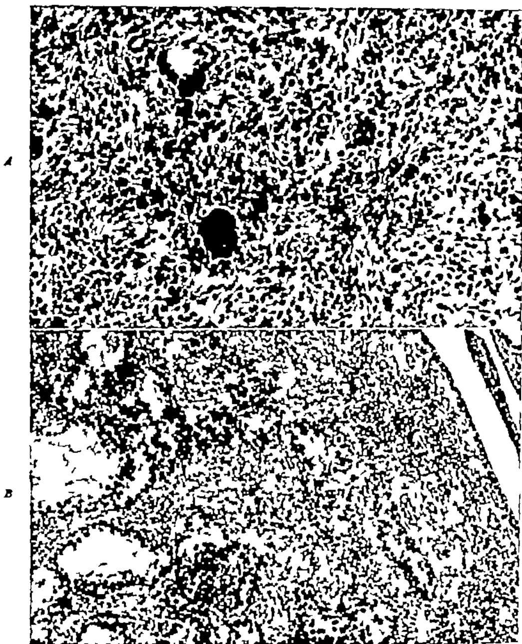


Fig 217—4 A field from a tendon-sheath nodule of a finger (pigmented nodular tenosynovitis or giant-cell tumor so-called) showing appreciable cellularity and the presence of occasional multinuclear cells. Many of the histiocytic stromal cells contained hemosiderin granules, nondiscernible at this magnification. (×100.) *B* A field from a lesion of pigmented villonodular synovitis of a knee joint showing prominent synovial lined spaces within the thickened synovial membrane. These apparently result from agglutination of villi and should not be misinterpreted as indicating the presence of synovial sarcoma. Other fields of this lesion showed appreciable collagenization, scattered multinuclear (giant) cells, and abundant hemosiderin deposition. (×125.) (From Lichtenstein L.: Tumors of Synovial Joints, Bursae, and Tendon Sheaths, Cancer 8: 816, 1955.)

change ensued Even the exuberant lesions in the knee joint that recurred after synovectomy were observed to clear up completely following roentgen ray therapy in relatively small dosage[18] which is scarcely the response one would expect if the lesion were a neoplasm.

This experience with the condition pointing to its benign character is apparently shared by De Santo and Wilson Jaffe and Selin, Ackerman and del Regato and others. It should be noted also that Young and Hudacek have reproduced some of the proliferative features of pigmented villonodular synovitis by inducing prolonged hemarthrosis in dogs under conditions of continued articular function. There has been some dissenting opinion in recent years, however that warrants close scrutiny with a view to clarifying the situation. Thus Bennett has implied that there may well be transitions between the condition under discussion (which he prefers to regard as a neoplasm of specialized synovial lining cells) and malignant synovial tumors and, collaterally that some synovial sarcomas may develop through malignant change in originally benign growths. From his reported case material, however one gathers that this interpretation is based largely upon inference rather than convincing follow up observations. Similarly, Ackerman, in qualifying a statement that "the lesion of pigmented villonodular synovitis and bursitis practically never becomes malignant" has cited a case in the files of the Armed Forces Institute of Pathology (No 177773) held to represent an instance in point arising in a prepatellar bursa, which recurred and subsequently metastasized. The recurrent neoplasm to judge by the available sections, was present within collagenous connective tissue (possibly tendon, ligament, fascia, or capsule) and extended beneath the skin. It was composed essentially of a malignant spindle-cell stroma and was characterized otherwise by its appreciable content of multinuclear cells. These on the whole resembled the osteoclast like macrophages commonly seen in lesions appearing in skeletal and paraskeletal sites. In any event, there was no proof that the tumor actually arose within a bursa as claimed or that it had developed through malignant change in a lesion of pigmented villonodular bursitis or tenosynovitis. Continuing Willis in a recent discussion agrees that the widespread brown, seaweed like synovial growths sometimes found filling a large joint (one expression of diffuse pigmented villonodular synovitis) are inflammatory and not neoplastic and that these frequently include small or large nodules closely resembling in structure the solitary "giant-cell growths." On the other hand, he feels that many of the solitary growths are neoplasms (benign synovioma) and attempts to explain this apparent contradiction by postulating that hyperplasia in these circumstances may at times pass insensibly into neoplasia.

Further M J Stewart and Wright are unequivocally committed to the neoplastic view The latter investigator in particular designates the condition under discussion as "benign giant-cell synovioma" and maintains that it may on occasion undergo malignant change and conversion to a special kind of synovial sarcoma, namely the "well-differentiated, giant-cell type of malignant synovioma" In his paper on malignant synovioma,[24] Wright includes two instances of this specific type (cases 43 and 44) situated in the knee and ankle regions respectively in which, after several unsuccessful attempts at local surgical extirpation, it was deemed necessary

to amputate the affected lower extremity It may be significant, however that the duration of symptoms prior to radical surgery was as long as 9 and 15 years, respectively and that both patients were well 6 years after amputation, despite the generally poor prognosis in cases of indubitable synovial sarcoma in which amputation is done as a late secondary procedure. Through the courtesy of Professors Willis and Stewart I have had the opportunity of studying representative sections of one of these lesions, and my impression is that the diagnosis of sarcoma was based not upon cytologic evidence of frank malignancy (the picture was essentially that of pigmented villonodular synovitis) but rather upon the finding that the lesion had substantially encroached upon the surrounding muscle tissue. As a token of malignancy this feature would be significant only if the lesion were an undisputed neoplasm, which brings us right back to the basic question in point.

The same problem in interpretation was highlighted by an unusual specimen that I had occasion to examine recently The patient in this instance was a young man 23 years old who, while in the service, had a biopsy of a lesion in a knee joint, which proved to be diffuse pigmented villonodular synovitis. The following year because of persistence of pain and swelling of the affected knee, he received roentgen-ray therapy at a military hospital the specific details of which are not available. Two years later the knee joint was explored at this hospital because of a palpable, painful mass in the posterior knee region. At surgery a firm lobulated fist-sized mass, situated beneath and slightly lateral to the head of the gastrocnemius muscle, was extirpated Because the question of aggressiveness was raised by the examining pathologist, it was deemed desirable to obtain wider clearance by removing portions of the gastrocnemius and soleus muscles, the contiguous head of the fibula, the periosteum of the posterior tibia, and the posterior portion of the capsule of the knee These structures, however failed to show evidence of involvement. The mass measured 8.5 x 7 0 x 5 0 cm. in its greatest dimensions and weighed 160 Gm. it was solid, firm lobulated, and tan-brown in color and was invested by a thin connective tissue capsule, except on its raw undersurface. Here, in places, the lesion was encroaching upon muscle tissue by direct continuity Thorough sampling of the mass showed the picture microscopically of pigmented nodular synovitis. The histiocytic stromal cells were of uniform appearance, contained abundant hemosiderin pigment, and presented only rare mitoses and no indication of nuclear atypism. It was felt that, although the lesion was encroaching upon muscle tissue by direct extension (not frank invasion) this in itself should not be construed as being indicative of a malignant or even of a neoplastic nature. Accordingly the recommendation was made that radical surgery was not indicated and that prophylactic irradiation (in small to moderate dosage) of the bed of the extirpated lesion might be of value in forestalling possible local recurrence. This could not be instituted promptly because of wound infection, but the patient has presented no evidence of local recurrence to date (3-year follow-up)

It should be noted also that on occasion lesions of pigmented villonodular synovitis of the knee and also of the hip joint may erode contiguous articular bone ends and even extend through such apertures into the interior of one or more bones, producing roentgenographically discernible defects. I have observed material

from two pertinent instances of hip joint involvement in which the proximal femur and acetabulum were penetrated and two of knee joint involvement, in which the distal femur and upper tibia were implicated. These cases responded satisfactorily to conservative treatment and the point is stressed that such direct extension into articular bone ends should not be construed as evidence of malignant change, disturbing as it may be to someone who observes it for the first time.



Fig 18.—Roentgenogram showing partial destruction of a terminal phalanx of a finger by a tendon sheath node.

In the case of tendon-sheath nodules of the nature of pigmented nodular tenosynovitis (so-called giant-cell tumor) it is well known that they also may induce pressure erosion of contiguous bones, especially phalanges of the fingers and toes (Fig 218) and occasionally even extend into such eroded bones. This complication was recently discussed by Fletcher and Horn, and the point was stressed that such erosion is fairly common, if one looks for it, and should not be construed in itself as an indication of neoplastic aggressiveness. Incidentally the interesting and rare tumor of a phalanx of a finger recently reported by Price and Valentine as a "malignant giant-cell synovioma" seems clearly to have originated within bone

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and, however one chooses to interpret it, is not an instance of a malignant tendon sheath tumor. Cognizance must be taken, however, of several case reports noting the rare occurrence of malignant change in tendon sheath growths having the pathologic character apparently of so-called giant-cell tumor. Thus, Kobak and Perlow have reported an instance of "xanthomatous giant-cell tumor" thought to originate near the tendinous insertion of the triceps at the elbow which recurred a number of times after local excision despite supplementary irradiation, also extended to the axillary lymph nodes, and within a year metastasized to the lungs and abdominal viscera. The authors point out that, while the cytologic picture "resembles closely a xanthomatous giant-cell tumor of tendon sheath origin," the stromal cells were obviously anaplastic and some of them presented atypical mitotic figures. The clinical behavior of this neoplasm, it may be added, is reminiscent of that of an aggressive synovial sarcoma. Another pertinent case published recently by Decker and Owen is that of a "giant cell tumor to tendon sheath" in the ankle region apparently of fourteen years duration prior to treatment, that recurred twice following surgical excision and, because of invasion and destruction of the tarsal bones, finally necessitated amputation of the leg, though too late to prevent metastases to the vertebral column and lung. In sections of the primary tumor cues to the recognition of aggressiveness were increased cellularity in places, fusiform shape of the stromal cells, and an appreciable number of mitotic figures. Conceivably there may be a few other instances in point not specifically mentioned here. At all events, the practical inference to be stressed is that, on rare occasions apparently a tendon-sheath node may undergo malignant change and hence require appropriate radical surgery without temporizing. On the other hand, it should be borne in mind that the overwhelming majority are innocuous and, if not neglected too long, may be effectively treated by conservative surgical excision.

BENIGN TUMORS

Hemangioma

Reports of benign neoplasms composed of blood vessels, developing within the capsules of large joints, particularly the knee joint, have been well documented, although they are distinctly uncommon. The relatively few recorded instances have been of the nature of either circumscribed or more widespread cavernous hemangiomas. As a representative example of localized involvement of the knee joint, one may cite the case reported by Osgood of an encapsulated, lobulated, reddish tumor mass that was attached by a pedicle to the infrapatellar fat pad. This growth measured 8 cm. in its greatest dimension and proved on pathologic examination to be a cavernous hemangioma. Its surgical extirpation was a simple task, and the patient, a 26-year-old woman who had complained of intermittent pain and disability for 8 years, was completely relieved.

In other instances, virtually the entire joint capsule may be permeated by tortuous, engorged, thin-walled blood vessels, some of which may be of rather large caliber and prone to rupture, so that copious bleeding seriously interferes with any attempt at surgical excision. For a comprehensive discussion of such diffuse

hemangiomas of the knee joint and particularly their clinical recognition and appropriate treatment one may turn to the paper of Bennett and Cobey which presents a survey of 29 cases including 5 of their own Cobey subsequently reported 4 additional pertinent cases. They pointed out that one may suspect the condition from the following findings intermittent pain and swelling of the affected joint (often present since childhood and tending to be induced or aggravated by trauma) reduction in size of the swelling on elevation of the affected limb and aspiration of blood from the affected joint The presence of a hemangioma elsewhere is another helpful cue With reference to treatment Bennett and Cobey expressed the view that complete surgical excision is feasible only when dealing with relatively small or pedunculated hemangiomas of the capsule For comparatively large or extensively ramifying hemangiomas, they favor roentgen ray therapy because of its effectiveness, as well as the hazards of serious hemorrhage impaired circulation and infection attendant upon attempts at complete surgical removal. In one of their earlier cases these complications led eventually to loss of a limb

It may be noted in passing that other pertinent papers dealing with hemangiomas of articular capsules and their surrounding structures are those of Weaver and of Sabrazes and his associates.

As for hemangiomas of bursae I have never encountered an unequivocal instance or found reference to one in the literature A limited number of hemangiomas developing within and about tendon sheaths have been recorded however Thus, Burman and Milgram collected some 10 cases in the literature and reported 6 additional instances, the majority of which however involved one or another tendon and the peritendinous tissue rather than the tendon sheath primarily The clinical picture in these cases was apparently too nondescript to permit of any accurate impression prior to surgical exploration. It is worth noting also that in several instances disconcerting bleeding occurred during the course of attempted excision of the vascular tumor suggesting that, as in dealing with ramifying hemangiomas of joints, it may be more expedient to resort to irradiation. The subject of hemangiomas of tendon sheath has also been discussed by Harkins, Bate and Webster and Geschickter among others.

It may be mentioned here that several lymphangiomas apparently developing in tendons and their sheaths have been recorded—two by Hugenin and Oberling and another by Faldini that was apparently somewhat more cellular being designated as a lymphangioendothelioma. From the meager data supplied in these reports, one can scarcely venture any helpful comment in regard to the clinical behavior of such tumors or their appropriate treatment.

Lipoma

Although it is conventional to list lipoma among the benign tumors affecting joints, its occurrence is distinctly unusual One must be circumspect, moreover about accepting casual mention of such observations at their face value, inasmuch as the subsynovial fat deposits may be rather thick normally especially in a large joint such as the knee joint, and constitute synovial-covered pads or folds that bulge into the joint cavity When a circumscribed protruding fatty mass shows

distinct branching lobulation, there appears to be a sounder basis for accepting it as a neoplasm, and such growths are usually designated as arborescent lipomas. The relatively few recorded lipomas of one type or another have been encountered mainly in the knee and ankle joints.[19]

The occurrence of fatty tumors in bursae has not been noted, to my knowledge. There are, however several well-documented papers dealing with fatty growths held to represent lipomas of tendon sheaths. Thus Strauss, in reporting a pertinent instance, collected some 18 cases from the literature that he accepted as genuine lipomas of either simple or arborescent type. From these data, Strauss inferred that such growths develop slowly over a period of years, eventually causing some pain and disability as well as obvious swelling and deformity of the affected part. He remarked further that their surgical excision may entail removal of the involved portion of the tendon sheath. Mason also, in discussing comparable growths in the hand specifically pointed out that the arborescent lipomas may take the form of numerous fatty villi developing along the course of the involved tendon sheath and that sometimes the tendon itself is thinned out or infiltrated by fat, so that partial resection of it is indicated. Among other pertinent references, those of Valdoni and of White may be cited. The latter in describing a remarkable instance of arborescent lipoma developing along the course of tendon sheaths in the ankle region observed that the shaggy fatty villi had spread not only over the parietal and visceral layers of the involved sheaths, but had also extended (after 7 years or more) into the neighboring joints and penetrated the periosteum of the contiguous tarsal bones.

It may be noted here in passing that in some older papers[34] dealing ostensibly with tumors of tendon sheaths one finds reference to lesions characterized by xanthomatous (cholesterol and cholesterol-ester) deposits in tendons. These are obviously a manifestation of xanthoma tuberosum multiplex, an inbred disorder of cholesterol metabolism, and, as such, are not germane to a discussion of neoplasms.

Other Benign Tumors

When one considers critically the incidence of benign connective-tissue tumors other than hemangioma and lipoma within joints, bursae, and tendon sheaths, one gets into rather dubious territory As noted, both fibroma and chondroma are also listed in some review articles[7, 27, 28] dealing with tumors of tendon sheaths particularly but unequivocal pathologic observations justifying their inclusion are singularly lacking In this connection, one must be certain that what is interpreted as a fibroma does not actually represent a solitary lesion of pigmented nodular synovitis or tenosynovitis that has undergone involutional scarring or collagenization in the wake of substantial necrosis. In a general discussion of tumors of tendon sheaths, Jaffe[23] remarked that there are a few authentic cases of fibroma on record, but the pertinent references were not cited. With respect to the hand specifically Mason expressed the opinion that fibromas may take origin from tendons and their sheaths, as well as from joint capsules and intermuscular septa, although he qualified this statement to the effect that these are quite rare and that many so diagnosed were probably neuromas.

As for so-called chondromas, I as noted adhere to the view of Freund and Fisher[14] that the condition of synovial or bursal chondromatosis represents a self limited metaplastic process. The same question of interpretation arises of course, in connection with sessile or pedicled "chondromas" developing in tendon sheaths. One must also take cognizance here of the comparatively rare instances recorded by Buxton and by Janik among others in which a single cartilage growth of appreciable size was found attached to a tendon sheath so that in the course of surgical extirpation, resection of the sheath was deemed essential Such cartilage growths appear actually to represent genuine neoplasms, but it is relevant to point out that, on occasion sizeable chondromas or chondrosarcomas may develop in the extraskeletal soft parts of extremities[18] without any relationship to tendon sheaths and that, by the same token proximity does not necessarily establish a site of origin Such subtleties, however seem not to have been duly considered by the authors of the papers cited and from the sketchily recorded pathologic data it is difficult to arrive at any independent judgment

MALIGNANT TUMORS

It is well known that malignant neoplasms of one type or another may extend into an articular capsule from a contiguous bone site. Thus osteogenic sarcoma, chondrosarcoma, and reticulum-cell sarcoma developing in the lower end of a femur for example often spread eventually into the capsule of a knee joint at its attachment to the articular bone end On the other hand, the only *primary* malignant tumor encountered with any degree of frequency in joints, as well as bursae and tendon sheaths, is the tumor that is appropriately designated as synovial sarcoma. As noted, the occurrence in these sites of other primary malignant tumors is so rare as to be of little practical moment The remainder of this discussion will deal therefore with synovial sarcoma, emphasizing particularly current problems in diagnosis and treatment.

Synovial Sarcoma

This is the designation that is preferred apparently by most investigators (synovial sarcomesothelioma synovial sarcoendothelioma, malignant synovioma, and synovialoma are some of the other names employed) The cytologic hallmark of this tumor whatever one chooses to call it, is the tendency of its primitive or mesenchymal spindle connective tissue cells to line spaces and ramifying clefts (presumably abortive joint spaces) Similarly in tissue-culture studies of a number of synovial sarcomas, Murray Stout, and Pogogeff observed that the tumor cells have the capacity to line slits or tubes and to secrete a mucinous substance, as well as to form strands of hyperchromatic fibrosarcoma-like cells supported by reticulin fibers. The over all picture is somewhat reminiscent of that of a malignant mesothelioma in that there is a pseudoepithelial component within a dominant sarcomatous stroma. It seems logical, however to maintain a sharp distinction between synovial sarcoma and mesothelioma, if only because the term "mesothelium" by anatomic definition is conventionally restricted to the layer of cells that lines the

coelom or body cavity of the embryo and subsequently the serous membranes of the peritoneum, pleura, and pericardium.

Synovial sarcoma though relatively uncommon as tumors of skeletal soft parts go is not so rare as it is sometimes held to be. Thus, Bennett[3] was able to study fully 32 instances treated in military hospitals during the late war Haagensen and Stout in a survey of the literature as of 1944 recorded as many as 9 instances from their own files and sizeable groups of cases have been reported from other clinics. Similarity I have had occasion to observe material from at least 12 cases seen *in consultation within recent years.*[33] *A generation ago synovial sarcomas* were often called "adenosarcomas" without full awareness apparently of their distinctive character and it is altogether probable that even today some pathologists still fail *to recognize instances of this neoplasm through unfamiliarity with its specific* features. Although pertinent case reports under whatever title date back about sixty years it is only in comparatively recent years that the serious clinical behavior of these tumors, the distinctive cytologic features leading to their identification, and the formidable problems entailed in their treatment have become subjects of common discussion. Among the papers in the American literature contributing materially to our understanding of synovial sarcomas have been those of Smith (1927) Knox (1936) De Santo and associates (1941) [11] Fisher (1942) [18] Haagensen and Stout (1944) and Bennett (1947) The keen discussion by Knox is particularly valuable for its pathologic insight, as well as its useful compilation and *critical analysis of the older literature, as is also the article by Fisher Much valuable* information was likewise elicited by Haagensen and Stout in a comprehensive survey of 104 cases, in which they attempted to analyze how the hitherto doleful results of treatment might be improved. Additional papers of value dealing with problems in therapy are those of Coley and Pierson, Briggs, Pack and Ariel, and Tillotson, McDonald and Janes, among others.

Clinical Features

Age and Sex Incidence.—Synovial sarcoma occurs in males more often than in females but the differential is not great enough to be of much help in diagnosis. Also it is observed most often in relatively young adults, although it is by no means unusual in adolescents or older adults and may in fact, develop at almost any age.

Localization.—With few exceptions synovial sarcomas are encountered in the extremities, and it is particularly the lower extremity that is predilected. The knee joint and the bursae in its vicinity account for a very considerable number Thus, nearly half of the tumors surveyed by Haagensen and Stout developed in the knee region. The foot and ankle region is another relatively common site. In the upper extremity the region of the hand and wrist constitute a favorite site of origin, although occasional instances are observed in the elbow and shoulder regions. It seems to me that detailed statistical analysis that goes beyond these rough estimates suffers of necessity from the limitations of random sampling Of the last 8 synovial sarcomas which I observed,[33] 3 developed in the foot (2 in the ankle region and 1 on the plantar aspect) 1 in the thigh above the knee, 2 in the

hand (1 in the palm and another in the capsule of an interphalangeal joint) 1 in the elbow region and 1 in the shoulder region On the other hand 4 tumors previously encountered[24] were all in the lower extremity involving a knee joint, an astragalocalcaneal joint, a bursa around an ankle and a popliteal bursa respectively

Nature and Duration of Clinical Complaints

It has been observed repeatedly that synovial sarcomas tend to develop insidiously and that rather paradoxically despite their serious nature ultimately several years may elapse before the patient is sufficiently concerned to seek surgical treatment. In the cases analyzed by Haagensen and Stout for example, the mean duration of symptoms preoperatively was estimated at 2.6 years, while instances in which the patient was aware of a growth as long as 4 or 5 years are not at all uncommon The presenting complaint is often that of a slowly enlarging swelling that is likely to be somewhat painful, especially on motion of the affected part. In some instances, a history of antecedent trauma may be elicited, but the significance of this appears rather doubtful. While these findings are likely to suggest the presence of a tumor the possibility of synovial sarcoma specifically is usually not suspected at the outset. In the case of relatively deep-seated tumors in the knee region, particularly the preoperative clinical impression may not be that of a neoplasm at all The practical import of this in relation to surgical management is considered further on.

Pathologic Characteristics

Gross Appearance.—Synovial sarcoma often presents as a circumscribed tumor at the time of initial surgical exploration. Occasionally it may already be widely infiltrating (e.g., in the sole of a foot) when first recognized. Also when it develops within the synovial lining of a large joint such as the knee joint, as it sometimes does, it tends to spread diffusely over the articular capsule The discrete growths are frequently comparatively small, measuring no more than 1 to 3 cm. in greatest dimension. The apparent encapsulation and limited size of such tumors are, of course, deceptive and altogether their gross appearance is hardly calculated to convey an impression of potential seriousness The neoplastic tissue on section may be grayish or more pink or yellow in color and its consistency likewise varies depending largely upon its mucin content and upon how fibrous its stroma happens to be. It should be noted also that some synovial sarcomas exhibit focal calcification, which may be roentgenographically discernible[23] Another suggestive lead to their recognition is the presence commonly of small clefts or cystlike spaces within the tumor containing viscid fluid As indicated, however the impression of synovial sarcoma is not often registered prior to microscopic examination, except perhaps as a shrewd surmise based largely upon the location of the tumor

A synovial sarcoma that has been neglected or that has recurred after unsuccessful surgical treatment may become obviously aggressive. Specifically it may invade the contiguous soft parts, extend into one or more of the adjacent bones, and eventually metastasize to the lungs and skeleton particularly It is noteworthy

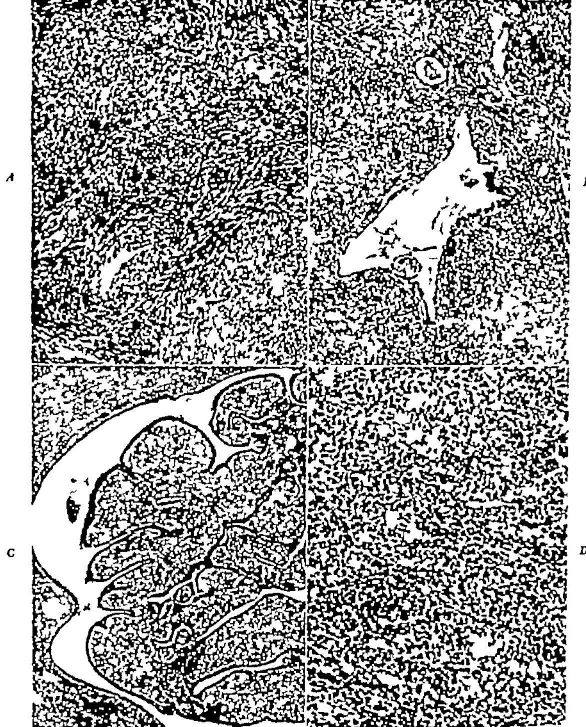
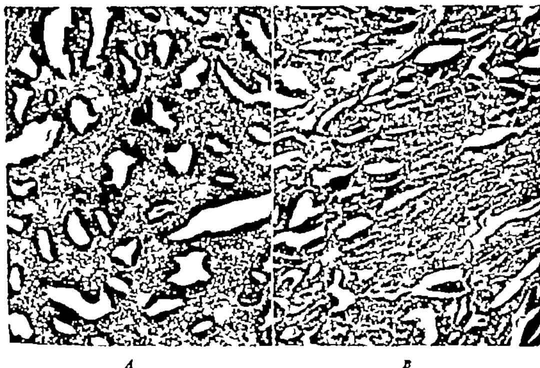


Fig 219—*A* The cytologic pattern characterizing the major portion of a synovial sarcoma situated in the palm of a hand. From this picture alone of decussating bundles of spindle cells, one could venture an impression of sarcoma though not necessarily of synovial sarcoma (×110) *B* Another field of the tumor illustrated in Fig 219 *A* showing the presence of smaller and larger spaces bordered by compacted tumor cells. The largest of these clefts also presents a telltale whorled papillary tuft. Fields such as this are indicative of synovial sarcoma but they were found only after many tissue blocks had been examined. (×110.) *C* Still another random field of the synovial sarcoma of the hand illustrated in *A* and *B* showing a comparatively large, invaginated tuft within a sinuous cleft. The tumor cells lining the spaces were compacted, flattened, and pseudoepithelial in appearance, as seen in higher magnification. (×80.) *D* Cytologic pattern characterizing the major portion of another synovial sarcoma. (×190.) (From Lichtenstein, L Tumors of Synovial Joints, Bursae, and Tendon Sheaths, Cancer 8: 816, 1955.)

also that the neoplasm exhibits a greater tendency to spread to regional lymph nodes than do most sarcomas of extremities[1, 40] (a factor that must be taken into account in appropriate treatment)

Microscopic Features

The distinctive features of synovial sarcomas and the variations in detail from case to case have been fully elaborated in a number of comparatively recent papers[3, 30, 33, 47] and for the sake of brevity one may forego reiteration of detail. Suffice it to emphasize here that synovial sarcoma is characterized cytologically by the presence in varying proportions, of two essential components (1) a richly



A *B*

Fig. 220 – Selected fields of a synovial sarcoma situated in the ankle region of an 18-year-old boy showing conspicuous pseudoglandular formation. Tumors such as this were formerly designated as adenosarcomas. At surgical exploration this neoplasm was thought to be an organizing hematoma and as such was incised and curetted (×81) (From Lichtenstein, L. Tumors of Synovial Joints, Bursae and Tendon Sheaths, Cancer 8, 816 1955)

cellular essentially spindle-cell stroma that frequently dominates the picture and that, in itself is likely to create an impression of a primitive fibrosarcoma and (2) random fields featuring peculiar clefts and/or glandlike structures lined by columnar or cuboidal cells, which may simulate epithelial lining cells (Figs. 219 and 220) As Haagensen and Stout have aptly remarked, the tumor is always composed of these two sharply contrasted tissue forms one resembling fibrosarcoma, the other reproducing caricatures of synovial structures, and the two are inextricably intermingled. When the specific synovial component is prominent, one

can readily understand the old designation of adenosarcoma, and, by the same token the diagnosis of synovial sarcoma should be fairly obvious to an observer familiar with the neoplasm (Fig 220) It is important to recognize, however that fields showing telltale sinuous clefts and glandlike spaces may be so sparsely distributed as to require the examination of many tissue blocks for their detection. In such instances an incisional biopsy specimen may well be inadequate for definitive diagnosis.

Treatment and Prognosis

As has been emphasized by many investigators, the results of treatment of synovial sarcoma to date have been discouraging on the whole, although it appears that some of the published cases were inadequately or injudiciously treated. Delay in recognition lack of a concerted plan of attack, temporizing and belated awareness of the seriousness of the tumor have all contributed to the picture of therapeutic failure. At present we are still striving for a rational approach to the situation. It must be frankly acknowledged however that the problem is inherently difficult, for we are dealing with a tumor whose behavior is treacherous and, in some respects, reminiscent of that of malignant melanoma. Despite the initial slow growth and circumscribed character of many synovial sarcomas, attempts at their surgical extirpation are followed in a high proportion of cases by local recurrence and extension and eventually by fatal dissemination, just as attempts to uproot an established bed of Oriental poppies may stimulate them to grow rampant through the garden like unrestrained weeds Furthermore, synovial sarcoma may exhibit a dismaying persistence in spite of therapy and is capable of cropping up after a quiescent interval of as long as 5 or 10 years or more so that one hesitates to speak even of a 10-year cure. Still another handicap in planning a therapeutic program is the lack of substantial detailed information going beyond general impressions in regard to the precise manner and rate of spread of the neoplasm, whether by fascial planes, lymphatics, or venous channels

It is small wonder therefore, that the prevailing view in regard to prognosis, even under favorable auspices, is a somber one brightened only by the consideration that the clinical course may be protracted many times over a period of several or many years. In fact, Haagensen and Stout were so pessimistic in their appraisal of the problem as to advocate immediate amputation as a routine procedure, even for synovial sarcomas that are relatively small and still circumscribed when first observed. Although fully recognizing the seriousness of the situation, I am inclined to regard this recommendation as a counsel of desperation, the necessity for which is far from proved at present. The remainder of this discussion will be devoted mainly to consideration of other less drastic measures that appear to be well conceived in the light of experience to date and deserving of further clinical trial. Whether we shall have to be content ultimately with a survival rate perhaps no higher than 25 per cent[40] because of the inherent nature of synovial sarcoma, or whether this can be increased under favorable auspices to a substantially higher estimate, can only be determined empirically

It seems to be true unfortunately that the outcome in many instances is irrevocably prejudiced by the initial surgical approach to the presenting tumor (Fig 220) and, in this connection the following suggestions may be advanced In dealing with any tumor in the soft parts of the hand or foot or in the vicinity of the knee elbow and shoulder joints particularly the possibility of synovial sarcoma should always be borne in mind, and it appears that even experienced surgeons may fail to anticipate this contingency By the same token in excising such tumors one must scrupulously avoid crushing (with clamps or forceps) inadvertent incision and especially blunt dissection Needless to say one should also strive for adequate clearance and block excision would be advantageous, but this may not be feasible because of location. It was precisely because of the hazard of dissemination entailed in the injudicious removal of the primary growth that Haagensen and Stout advocated carefully performed incisional biopsy While this recommendation may be well conceived theoretically it seems to me to be unrealistic. For reasons already indicated, the likelihood is that section of a single sliver of tumor tissue selected at random would not provide an unequivocal diagnosis of synovial sarcoma unless the pathologist were particularly fortunate as well as astute (Fig 219 *A B* and *C*)

The value of postoperative roentgen ray irradiation of the tumor bed with a view to destroying any residual tumor nests that may be present at the periphery of the extirpated growth seems to be borne out clearly by our analysis[34] of the follow-up data available in the literature While this view tends to controvert the much repeated statement that roentgen ray therapy for synovial sarcoma is of little avail except perhaps for palliation its validity is supported on the other hand, by the clinical observations of Briggs and of Pack and Ariel. The time factor is important however and local irradiation should be started as soon as possible if it is to be effective In view of the significantly high incidence of lymphatic extension, attention should also be directed promptly to the regional lymph nodes, both proximal and distal Even if these are not palpably enlarged, the suggestion is ventured that prophylactic irradiation be employed for its possible benefit, and this should probably be pushed to the limit of skin tolerance If enlarged regional *lymph nodes are detected surgical excision of the involved group may* be preferred,[1] and, in this connection, one must consider the recommendation of Pack and Ariel of dissection in continuity to encompass the intervening lymphatics, such as one might for extension of a malignant melanoma. In the face of a threat to the last effective barrier to uncontrollable dissemination, it would seem that one must accept the hazard of lymphedema of the affected extremity as a calculated risk.

The problem of coping with a tumor that recurs despite these therapeutic measures is formidable though by no means hopeless. Needless to say if it flourishes as a rapidly growing frankly invasive neoplasm, one must have prompt recourse to amputation of the affected limb at an appropriate level provided, of course that the tumor has not already spread beyond bounds. In dealing with such aggressive tumors, the prognosis should be guarded, in spite of amputation. If on the other hand, as in some observed cases, the recurrent growth is still discrete and relatively small whether it be in the original surgical field or somewhat removed

from it, one may resort again to meticulous excision prompt supplementary roentgen-ray irradiation of the tumor bed, investigation of the regional lymph nodes if this has not already been done, and of course continued close follow-up The question may be justifiably raised at this point of whether the patient is not placed in jeopardy by pursuing a conservative course for a recurrent malignant neoplasm. A recommendation of amputation under these circumstances would be justified however only if it offered a brighter prospect for cure, and thus far at least the recorded experience does not indicate convincingly that ablation of the affected limb is an attractive alternative.

In the event that a synovial sarcoma is already frankly invasive when first encountered, or if it is not amendable to surgical extirpation because of its bulk or spread over a joint capsule, because it has already enveloped major vessels and nerves, or for whatever reason, one has no alternative but to resort to ablation of the affected part without undue delay (provided that there is no roentgen-ray evidence of metastasis) It seems worth while in such instances, if only to give the patient the benefit of every possible doubt, to supplement radical surgery with an attack on the regional lymph nodes, either by irradiation or surgical excision, whether or not these are obviously involved clinically

At all events, in dealing with any particular instance, a note of distinct caution as to prognosis is in order for synovial sarcomas, as indicated, have been known to metastasize after a latent period of as long as 10 years or more.

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